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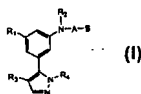
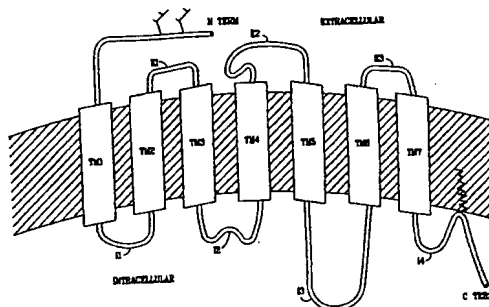
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(54) Title: SMALL MOLECULE MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE PROPHY-
LAXIS AND TREATMENT OF DISORDERS RELATED THERETO

(57) Abstract: The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Formula (I): Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D₂ receptor antagonist such as haloperidol, administered separately or together.



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**SMALL MOLECULE MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR
USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS
RELATED THERETO**

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FIELD OF THE INVENTION

10 The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot
15 formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders.

20 The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D₂ receptor antagonist such as haloperidol, administered separately or together.

BACKGROUND OF THE INVENTION

I. G protein-coupled receptors

25 [0001] G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. The transmembrane helices are joined by strands of amino acids having a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop, composed primarily of hydrophilic amino acids, joins transmembrane helices five
30 and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space. It is thought that the loop joining helices five and six, as well as, the carboxy terminus, interact with the G protein. Currently, G_q, G_s, G_i and G_o are G proteins that have been identified. The general structure of G protein-coupled receptors is shown in Figure 1.

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[0002] Under physiological conditions, G protein-coupled receptors exist in the cell membrane in equilibrium between two different states or conformations: an "inactive" state and an "active" state. As shown schematically in Figure 2, a receptor in an inactive state is unable to link to the intracellular transduction pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway and produces a biological response.

[0003] A receptor may be stabilized in an active state by an endogenous ligand or an exogenous agonist ligand. Recent discoveries such as, including but not exclusively limited to, modifications to the amino acid sequence of the receptor provide means other than ligands to stabilize the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of a ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

Serotonin receptors

[0004] Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein-coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite, neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders. With respect to on anti-psychotic treatment approaches focused on the serotonin receptors, these types of therapeutics can generally be divided into two classes, the "typical" and the "atypical." Both have anti-psychotic effects, but the typicals also include concomitant motor-related side effects (extra pyramidal syndromes, *e.g.*, lip-smacking, tongue darting, locomotor movement, etc). Such side effects are thought to be associated with the compounds interacting with other receptors, such as the human dopamine D2 receptor in the nigro-striatal pathway. Therefore, an atypical treatment is preferred. Haloperidol is considered a typical anti-psychotic, and clozapine is considered an atypical anti-psychotic.

[0005] Serotonin receptors are divided into seven subfamilies, referred to as 5-HT1 through 5-HT7, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT2 subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The human 5-HT_{2C} receptor was first isolated and cloned in 1987, and the human 5-HT_{2A} receptor was first isolated and cloned in 1990. These two receptors are thought to be the site of action of hallucinogenic drugs. Additionally, antagonists to the 5-HT_{2A} and 5-HT_{2C} receptors are believed to be useful in treating depression, anxiety, psychosis, and eating disorders.

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[0006] U.S. Patent Number 4,985,352 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{1C} receptor (now known as the 5-HT_{2C} receptor). U.S. Patent Number 5,661,012 describes the isolation, characterization, and expression of a functional cDNA clone encoding the entire human 5-HT_{2A} receptor.

5 [0007] Mutations of the endogenous forms of the rat 5-HT_{2A} and rat 5-HT_{2C} receptors have been reported to lead to constitutive activation of these receptors (5-HT_{2A}: Casey, C. *et al.* (1996) *Society for Neuroscience Abstracts*, 22:699.10, hereinafter "Casey"; 5-HT_{2C}: Herrick-Davis, K., and Teitler, M. (1996) *Society for Neuroscience Abstracts*, 22:699.18, hereinafter "Herrick-Davis 1"; and Herrick-Davis, K. *et al.* (1997) *J. Neurochemistry* 69(3): 1138, hereinafter "Herrick-Davis-2"). Casey describes a mutation of the cysteine residue at position 322 of the rat 5-HT_{2A} receptor to lysine (C322K), glutamine (C322Q), and arginine (C322R) which reportedly led to constitutive activation. Herrick-Davis 1 and Herrick-Davis 2 describe mutations of the serine residue at position 312 of the rat 5-HT_{2C} receptor to phenylalanine (S312F) and lysine (S312K), which reportedly led to constitutive activation.

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SUMMARY OF THE INVENTION

[0008] The present invention relates to non-endogenous, constitutively activated forms of the human 5-HT_{2A} and human 5-HT_{2C} receptors and various uses of such receptors. Further disclosed are small molecule modulators of these receptors. Most preferably, these modulators have inverse agonist characteristics at the receptor.

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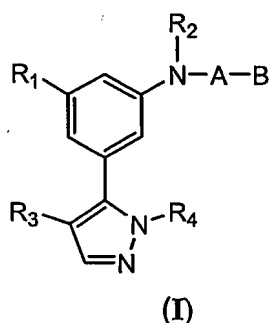
[0009] More specifically, the present invention discloses nucleic acid molecules and the proteins for three non-endogenous, constitutively activated human serotonin receptors, referred to herein as, AP-1, AP-3, and AP-4. The AP-1 receptor is a constitutively active form of the human 5-HT_{2C} receptor created by an S310K point mutation. The AP-3 receptor is a constitutively active form of the human 5-HT_{2A} receptor whereby the intracellular loop 3 (IC3) portion and the cytoplasmic-tail portion of the endogenous human 5-HT_{2A} receptor have been replaced with the IC3 portion and the cytoplasmic-tail portion of the human 5-HT_{2C} receptor. The AP-4 receptor is a constitutively active form of the human 5-HT_{2A} receptor whereby (1) the region of the intracellular third loop between the proline of the transmembrane 5 region (TM5) and the proline of TM6 of the endogenous human 5-HT_{2A} receptor has been replaced with the corresponding region of the human 5-HT_{2C} receptor (including a S310K point mutation); and (2) the cytoplasmic-tail portion of the endogenous human 5-HT_{2A} receptor has been replaced with the cytoplasmic-tail portion of the endogenous human 5-HT_{2C} receptor.

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[0010] The invention also provides assays that may be used to directly identify candidate compounds as agonists, partial agonists or inverse agonists to non-endogenous, constitutively activated human serotonin receptors; such candidate compounds can then be utilized in pharmaceutical composition(s) for treatment of diseases and disorders which are related to the human 5-HT_{2A} and/or human 5-HT_{2C} receptors.

[0011] The invention also provides compounds that exhibit high selectivity 5-HT_{2A} activity. More specifically, the compounds possessing 5-HT_{2A} receptor activity are designated by the general Formula (I):



10 wherein:

i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

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R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3 , OCF_3 , OEt, CCl_3 , Me, NO_2 , OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10} , COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

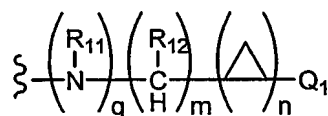
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is $C(=O)$, $C(=S)$ or SO_2 ;

vi) B is L_1 or L_2 ;

L_1 is:



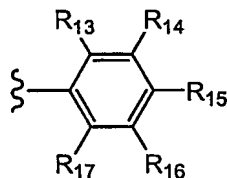
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of

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5 said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

10 L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or
15 a pharmaceutically acceptable salt.

[0012] These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

20 BRIEF DESCRIPTION OF THE DRAWINGS

[0013] In the following figures, bold typeface indicates the location of the mutation in the non-endogenous, constitutively activated receptor relative to the corresponding endogenous receptor.

[0014] **Figure 1** shows a generalized structure of a G protein-coupled receptor with the numbers assigned to the transmembrane helices, the intracellular loops, and the extracellular loops.

25 [0015] **Figure 2** schematically shows the active and inactive states for a typical G protein-coupled receptor and the linkage of the active state to the second messenger transduction pathway.

[0016] **Figure 3a** provides the nucleic acid sequence of the endogenous human 5-HT_{2A} receptor (SEQ.ID.NO.:22).

[0017] **Figure 3b** provides the corresponding amino acid sequence of the endogenous human
30 5-HT_{2A} receptor (SEQ.ID.NO.:23).

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[0018] Figure 4a provides the nucleic acid sequence of the endogenous human 5-HT_{2C} receptor (SEQ.ID.NO.:24).

[0019] Figure 4b provides the corresponding amino acid sequence of the endogenous human 5-HT_{2C} receptor (SEQ.ID.NO.:25).

5 [0020] Figure 5a provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2C} receptor ("AP-1 cDNA" - SEQ.ID.NO.:26).

[0021] Figure 5b provides the corresponding amino acid sequence of the AP-1 cDNA ("AP-1" - SEQ.ID.NO.:27).

10 [0022] Figure 6a provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2A} receptor whereby the IC3 portion and the cytoplasmic-tail portion of the endogenous 5-HT_{2A} receptor have been replaced with the IC3 portion and the cytoplasmic-tail portion of the human 5-HT_{2C} receptor ("AP-3 cDNA" - SEQ.ID.NO.:28).

[0023] Figure 6b provides the corresponding amino acid sequence of the AP-3 cDNA ("AP-3" - SEQ.ID.NO.:29).

15 [0024] Figure 6c provides a schematic representation of AP-3, where the dashed-lines represent the portion obtained from the human 5-HT_{2C} receptor.

20 [0025] Figure 7a provides the nucleic acid sequence of a constitutively active form of the human 5-HT_{2A} receptor whereby (1) the region of the between the proline of TM5 and the proline of TM6 of the endogenous human 5-HT_{2A} receptor has been replaced with the corresponding region of the human 5-HT_{2C} receptor (including a S310K point mutation); and (2) the cytoplasmic-tail portion of the endogenous 5-HT_{2A} receptor has been replaced with the cytoplasmic-tail portion of the endogenous human 5-HT_{2C} receptor ("AP-4 cDNA" - SEQ.ID.NO.:30).

[0026] Figure 7b provides the corresponding amino acid sequence of the AP-4 cDNA ("AP-4" - SEQ.ID.NO.:31).

25 [0027] Figure 7c provides a schematic representation of the mutated 5-HT_{2A} receptor of Figure 7b where the dashed-lines represent the portion obtained from the human 5-HT_{2C} receptor.

[0028] Figure 8 is a representation of the preferred vector, pCMV, used herein.

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[0029] Figure 9 is a diagram illustrating (1) enhanced (^{35}S)GTP γ S binding to membranes prepared from COS cells expressing the endogenous human 5-HT $_2\text{C}$ receptor in response to serotonin, and (2) inhibition by mianserin using wheatgerm agglutinin scintillation proximity beads. The concentration of (^{35}S)GTP γ S was held constant at 0.3 nM, and the concentration of GDP was held at 1 μM . The concentration of the membrane protein was 12.5 μg .

[0030] Figure 10 is a diagram showing serotonin stimulation of (^{35}S)GTP γ S binding to membranes expressing AP-1 receptors in 293T cells and the inhibition by 30 μM mianserin on WallacTM scintistrips.

[0031] Figures 11A and 11B are diagrams showing the effects of protein concentration on (^{35}S)GTP γ S binding in membranes prepared from 293T cells transfected with the endogenous human 5-HT $_2\text{C}$ receptors and AP-1 receptors compared to cells transfected with the control vector (pCMV) alone in the absence (Figure 11A) and presence (Figure 11B) of 10 μM serotonin. The radiolabeled concentration of (^{35}S)GTP γ S was held constant at 0.3 nM, and the GDP concentration was held constant at 1 μM . The assay was performed on 96-well format on WallacTM scintistrips.

[0032] Figure 12 provides bar-graph comparisons of inositol tris-phosphate ("IP3") production between the endogenous human 5-HT $_{2A}$ receptor and AP-2, a mutated form of the receptor.

[0033] Figure 13 provides bar-graph comparisons of inositol tris-phosphate ("IP3") production between the endogenous human 5-HT $_{2A}$ receptor and AP-4, a mutated form of the receptor.

[0034] Figure 14 provides bar graph comparisons of IP3 production between the endogenous human 5-HT $_{2A}$ receptor and AP-3, a mutated form of the receptor.

[0035] Figure 15 provides bar-graph comparisons of IP3 production between the endogenous human 5-HT $_{2C}$ receptor and AP-1.

[0036] Figures 16A-C provides representative autoradiograms showing displacement of I¹²⁵-LSD from brain sections by spiperone and Compound 1.

[0037] Figures 17A-C show *in vivo* response of animals to Compound 2 exposure.

DEFINITIONS

[0038] The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict
 5 with other definitions for these terms, the following definitions shall control.

[0039] AGONISTS shall mean moieties that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

[0040] AMINO ACID ABBREVIATIONS used herein are set out in TABLE 1:

TABLE 1

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M
PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

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- [0041] PARTIAL AGONISTS shall mean moieties which activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.
- 5 [0042] ANTAGONIST shall mean moieties that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.
- 10 [0043] CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) which is amenable to a screening technique.
- [0044] COMPOSITION shall mean a material comprising at least two compounds or two components; for example, and not limitation, a Pharmaceutical Composition is a Composition.
- [0045] COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity.
- 15 [0046] CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to constitutive receptor activation.
- [0047] CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.
- 20 [0048] CONTACT or CONTACTING shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.
- [0049] ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor" shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus.
- 25 [0050] In contrast, the term NON-ENDOGENOUS in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For

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example, and not a limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

- 5 [0051] INHIBIT or INHIBITING, in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

- [0052] INVERSE AGONISTS shall mean moieties that bind the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular
10 response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

- 15 [0053] LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

- [0054] As used herein, the terms MODULATE or MODULATING shall mean to refer to an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule. For example, Compounds which modulate/capable of modulating the 5-HT_{2A} activity
20 include agonists, inverse agonists, antagonists, inhibitors, activators, and compounds which directly or indirectly affect regulation of the 5-HT_{2A} activity.

- [0055] PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will
25 understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

- [0056] STIMULATE or STIMULATING, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

DETAILED DESCRIPTION

[0057] In addition to the foregoing beneficial uses for the modulators of 5-HT_{2A} receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

USE OF THE COMPOUNDS OF THE INVENTION

1. Antiplatelet Therapies (5-HT_{2A} mediated platelet aggregation):

10 [0058] Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

[0059] In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

[0060] A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

20 [0061] Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

[0062] Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation blood clots that cause first or second strokes.

[0063] Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

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[0064] Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

5 [0065] Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the
10 heart and traveling to the brain (embolism).

[0066] 5-HT_{2A} receptors are expressed on smooth muscle of blood vessels and 5-HT secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy. See Satimura, K, et al., Clin Cardiol 2002 Jan. 25
15 (1):28-32; and Wilson, H.C et al., Thromb Haemost 1991 Sep 2;66(3):355-60.

[0067] The 5-HT_{2A} inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limitation, the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing
20 platelet aggregation in a patient in need thereof comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of said treatment, comprising administering to said patient a composition comprising a
25 5-HT_{2A} inverse agonist disclosed herein.

[0068] In further embodiments, the present invention provides methods for reducing risk of blood clot formation in a angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to a said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

30 2. Asthma

[0069] It has been suggested that 5-HT (5-hydroxytryptamine) plays a role in the pathophysiology of acute asthma. See Cazzola, M. and Matera, M.G., TIPS, 2000, 21, 13; and De

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Bie, J.J. et al., British J. Pharm., 1998, 124, 857-864. The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of said treatment, comprising administering to said patient a composition comprising a
5 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of said treatment, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

3. Agitation

[0070] Agitation is a well-recognized behavioral syndrome with a range of symptoms,
10 including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield J, and Billig, N., (1986), Agitated Behaviors in the Elderly. I. A Conceptual Review. J Am Geriatr Soc 34(10): 711-721).

[0071] Agitation is a common occurrence in the elderly and often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are
15 degenerative diseases of the nervous system and by diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce dementia. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss E, et al., (1997), Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord
20 11(suppl 2):S45-S50).

[0072] An estimated five percent of people aged 65 and older and up to 20 percent of those aged 80 and older are affected by dementia. Of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

[0073] Agitated behaviors can also be manifested in cognitively intact elderly people and by
25 those with psychiatric disorders other than dementia

[0074] Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I.R., et al., J Clin Psychiatry 1999 Feb., 60(2):107-115; and Street, J.S., et al.,
30 Arch Gen Psychiatry 2000 Oct., 57(10):968-976).

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[0075] The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments, the agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimers disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including without limitation stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to said patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

15

4. Add-on therapy to Haloperidol in the treatment of schizophrenia and other disorders:

[0076] Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms, progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder. (See, American Statistical and Diagnostic Handbook).

[0077] Haloperidol (Haldol) is a potent dopamine D2 receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5-HT_{2A} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

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[0078] Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5-HT_{2A} inverse agonists disclosed herein with haloperidol also will provide benefits in these indications.

[0079] In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

[0080] In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to said patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

[0081] In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

[0082] In some embodiments, the present invention provides methods for treating infantile autism, huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

[0083] In further embodiments, the present invention provides methods for treating schizophrenia in a patient in need of said treatment comprising administering to said patient a dopamine D2 receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D2 receptor antagonist is haloperidol.

[0084] The administration of the dopamine D2 receptor antagonist can be concomitant with administration of the 5-HT_{2A} inverse agonist, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious

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reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the 5-HT_{2A} inverse agonist are administered in a single dosage form, and in other embodiments, they are administered in separate dosage forms.

[0085] The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from said schizophrenia, comprising administering to said patient a 5-HT_{2A} inverse agonist as disclosed herein.

PARTICULARLY PREFERRED MUTATIONS

[0086] For convenience, the sequence information regarding the non-endogenous, constitutively active human 5-HT_{2A} and 5-HT_{2C} receptors are referred to by identifiers as set forth in TABLE 2:

TABLE 2

IDENTIFIER	RECEPTOR	SEQ.ID.NO.:	FIGURE
AP-1 cDNA	5-HT _{2C}	28	5a
AP-1	5-HT _{2C}	29	5b
AP-3 cDNA	5-HT _{2A}	30	6a
AP-3	5-HT _{2A}	31	6b
AP-4 cDNA	5-HT _{2A}	32	7a
AP-4	5-HT _{2A}	33	7b

As will be discussed in greater detail below, a mutation analogous to that reported by Casey (C322K) was utilized in the human 5-HT_{2A} receptor and is referred to herein as AP-2. However, AP-2 did not lead to sufficient constitutive activation to allow for utilization in screening techniques.

INTRODUCTION

[0087] While it is sometimes possible to make predictions as to the effect of nucleic acid manipulation from one species to another, this is not always the case. The results reported by Casey suggest that a point mutation in the rat 5-HT_{2A} receptor evidences constitutive activation of the mutated receptor. Casey reports that the C322K mutation was approximately four fold more active than the native rat 5-HT_{2A} receptor. However, for purposes of a most preferred use, i.e., screening of candidate compounds, this corresponding mutation in the human 5-HT_{2A} receptor had little

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discernable effect in evidencing constitutive activation of the human receptor. This, of course, creates the reasonable conclusion that the information reported in Herrick-Davis 1 or Herrick-Davis 2 is of limited predictive value relative to the manipulation of the human 5-HT_{2C} receptor. Consequently, the ability to make reasonable predictions about the effects of mutations to the rat 5-HT receptors vis-à-vis the corresponding human receptors is not possible. Nonetheless, this unfortunate lack of reasonable predictability provides the opportunity for others to discover mutations to the human 5-HT receptors that provide evidence of constitutive activation.

[0088] Therefore, the present invention is based upon the desire of defining mutated sequences of the human serotonin receptors 5-HT_{2A} and 5-HT_{2C} whereby such mutated versions of the expressed receptor are constitutively active. These constitutively active receptors allow for, inter alia, screening candidate compounds.

[0089] What has been discovered and disclosed herein is that substantial activation of the human 5-HT_{2A} receptor can be obtained by "domain swapping," i.e., by switching the third intracellular domain of the 5-HT_{2A} receptor with the third intracellular domain of the 5-HT_{2C} receptor. Additionally, swapping the cytoplasmic tail of the two receptors further increases the IP₃ response. Furthermore, mutation of the serine at position 310 to lysine (S31OK) of the human 5-HT_{2C} receptor leads to constitutive activation.

[0090] What follows is a most preferred approach to identification of candidate compounds; those in the art will readily appreciate that the particular order of screening approaches, and/or whether or not to utilize certain of these approaches, is a matter of choice. Thus, the order presented below, set for presentational efficiency and for indication of the most preferred approach utilized in screening candidate compounds, is not intended, nor is to be construed, as a limitation on the disclosure, or any claims to follow.

25 **GENERIC G PROTEIN-COUPLED RECEPTOR SCREENING ASSAY TECHNIQUES**

[0091] When a G protein receptor becomes constitutively active, it binds to a G protein (Gq, Gs, Gi, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, (³⁵S)GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that (³⁵S)GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among

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other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor. .

5

CONFIRMATION OF G PROTEIN-COUPLED RECEPTOR SITE SCREENING ASSAY TECHNIQUES

[0092] Once candidate compounds are identified using the “generic” G protein-coupled receptor assay (*i.e.* an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the “generic” assay may not bind to the receptor, but may instead merely “uncouple” the G protein from the intracellular domain. Thus, by further screening those candidate compounds, which have been identified using a “generic” assay in an agonist and/or antagonist competitive binding assay, further refinement in the selection process is provided.

[0093] Lysergic acid diethylamide (LSD) is a well-known agonist of the 5-HT_{2A} and 5-HT_{2C} receptors, while mesulergine is a well-known antagonist to the 5-HT_{2C} receptor. Accordingly, in most preferred embodiments, an agonist (LSD) and/or antagonist (mesulergine) competitive binding assay(s) is used to further screen those compounds selected from the “generic” assay for confirmation of serotonin receptor binding.

20

SPECIFIED G PROTEIN ASSAY TECHNIQUES

[0094] The art-accepted physiologically mediated pathway for the human 5-HT_{2A} and 5-HT_{2C} receptors is via Gq. Intracellular accumulation of IP3 can be used to confirm constitutive activation of these types of Gq coupled receptors (see Herrick-Davis-1). As a result, “IP3 accumulation” assays can be used to further screen those compounds selected from an agonist and/or antagonist competitive binding assay. .

25

PHARMACEUTICAL COMPOSITIONS

[0095] Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-

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acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

EXAMPLES

- 5 **[0096]** The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. It is intended that equivalent, non-endogenous, constitutively activated human serotonin receptor sequences include
10 those having eighty-five percent (85%) homology, more preferably having ninety percent (90%) homology, and most preferably having ninety-five percent (95%) homology to the disclosed and claimed sequences all fall within the scope of any claims appended hereto.

EXAMPLE 1

- 15 **GENERATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED
HUMAN SEROTONIN RECEPTORS 5-HT_{2C} AND 5-HT_{2A}**

A. Construction of constitutively active 5-HT_{2C} receptor cDNA

1. Endogenous Human 5-HT_{2C}

- 20 **[0097]** The cDNA encoding endogenous human 5-HT_{2C} receptor was obtained from human brain poly-A⁺ RNA by RT-PCR. The 5' and 3' primers were derived from the 5' and 3' untranslated regions and contained the following sequences: .

5'-GACCTCGAGGTTGCTTAAGACTGAAGCA-3' (SEQ.ID.NO.:1)

5'-ATTCTAGACATATGTAGCTTGTACCGT-3' (SEQ.ID.NO.:2)

- 25 PCR was performed using either TaqPlusTM precision polymerase (Stratagene) or rTthTM polymerase (Perkin Elmer) with the buffer systems provided by the manufacturers, 0.25 μM of each primer, and 0.2 mM of each of the four (4) nucleotides. The cycle condition was 30 cycles of 94°C for 1 minute, 57 °C for 1 minute and 72 °C for 2 minutes. The 1.5 kb PCR fragment was digested with Xho I and Xba I and subcloned into the Sal I-Xba I site of pBluescript.

- 30 **[0098]** The derived cDNA clones were fully sequenced and found to correspond to published sequences.

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2. AP-1 cDNA

[0099] The cDNA containing a S310K mutation (AP-1 cDNA) in the third intracellular loop of the human 5-HT_{2C} receptor was constructed by replacing the Sty I restriction fragment containing amino acid 310 with synthetic double stranded oligonucleotides encoding the desired mutation. The sense strand sequence utilized had the following sequence:

5'-CTAGGGGCACCATGCAGGCTATCAACAATGAAAGAAAAGCTAAGAAAGTC-3'

(SEQ.ID.NO.:3)

and the antisense strand sequence utilized had the following sequence:

5'-CAAGGACTTTCTTAGCTTTTCTTTCATTGTTGATAGCCTGCATGGTGCCC-3'

10 (SEQ.ID.NO.:4).

B. Construction of constitutively active 5-HT_{2A} receptor cDNA

1. Endogenous Human 5-HT_{2A}

[0100] The cDNA encoding endogenous human 5-HT_{2A} receptor was obtained by RT-PCR using human brain poly-A⁺ RNA; a 5' primer from the 5' untranslated region with a Xho I restriction site:

5'-GACCTCGAGTCCTTCTACACCTCATC-3' (SEQ.ID.NO.:5)

and a 3' primer from the 3' untranslated region containing an Xba I site:

5'-TGCTCTAGATTCCAGATAGGTGAAAA CTTG-3' (SEQ.ID.NO.:6).

20 PCR was performed using either TaqPlusTM precision polymerase (Stratagene) or rTthTM polymerase (Perkin Elmer) with the buffer systems provided by the manufacturers, 0.25 μM of each primer, and 0.2 mM of each of the four (4) nucleotides. The cycle condition was 30 cycles of 94°C for 1 minute, 57°C for 1 minute, and 72 °C for 2 minutes. The 1.5 kb PCR fragment was digested with Xba I and subcloned into the Eco RV-Xba I site of pBluescript.

25 [0101] The resulting cDNA clones were fully sequenced and found to encode two amino acid changes from the published sequences. The first change is a T25N mutation in the N-terminal extracellular domain and the second change is an H452Y mutation. These mutations are likely to represent sequence polymorphisms rather than PCR errors since the cDNA clones having the same two mutations were derived from two independent PCR procedures using Taq polymerase from two different commercial sources (TaqPlusTM Stratagene and rTthTM Perkin Elmer).

2. Human 5-HT_{2A} (C322K; AP-2)

[0102] The cDNA containing the point mutation C322K in the third intracellular loop was constructed by using the Sph I restriction enzyme site, which encompasses amino acid 322. For the PCR procedure, a primer containing the C322K mutation:

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5'-CAAAGAAAGTACTGGGCATCGTCTTCTTCCT-3' (SEQ.ID.NO.:7)

was used along with the primer from the 3' untranslated region set forth above as **SEQ.ID.NO.:6**. The resulting PCR fragment was then used to replace the 3' end of the wild type 5-HT_{2A} cDNA by the T4 polymerase blunted Sph I site. PCR was performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer and 10% DMSO, 0.25 mM of each primer, 0.5mM of each of the 4 nucleotides. The cycle conditions were 25 cycles of 94°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute.

3. AP-3 cDNA

[0103] The human 5-HT_{2A} cDNA with intracellular loop 3 (IC3) or IC3 and cytoplasmic tail replaced by the corresponding human 5-HT_{2C} cDNA was constructed using PCR-based mutagenesis.

(a) Replacement of IC3 Loop

[0104] The IC3 loop of human 5-HT_{2A} cDNA was first replaced with the corresponding human 5-HT_{2C} cDNA. Two separate PCR procedures were performed to generate the two fragments, Fragment A and Fragment B, that fuse the 5-HT_{2C} IC3 loop to the transmembrane 6 (TM6) of 5-HT_{2A}. The 237 bp PCR fragment, Fragment A, containing 5-HT_{2C} IC3 and the initial 13 bp of 5-HT_{2A} TM6 was amplified by using the following primers:

5'-CCGCTCGAGTACTGCGCCGACAAGCTTTGAT-3' (SEQ.ID.NO.:8)

5'-CGATGCCCAGCACTTTCGAAGCTTTCTTTCATTGTTG-3' (SEQ.ID.NO.:9)

The template used was human 5-HT_{2C} cDNA.

[0105] The 529 bp PCR fragment, Fragment B, containing the C-terminal 13 bp of IC3 from 5-HT_{2C} and the C-terminal of 5-HT_{2A} starting at beginning of TM6, was amplified by using the following primers:

5'-AAAAGCTTCGAAAGTGCTGGGCATCGTCTTCTTCCT-3' (SEQ.ID.NO.:10)

5'-TGCTCTAGATTCCAGATAGGTGAAAAGTTG-3' (SEQ.ID.NO.:11)

The template used was human 5-HT_{2A} cDNA.

[0106] Second round PCR was performed using Fragment A and Fragment B as co-templates with **SEQ.ID.NO.:8** and **SEQ.ID.NO.:11** (it is noted that the sequences for **SEQ.ID.NOS.:6** and **11** are the same) as primers. The resulting 740 bp PCR fragment, Fragment C, contained the IC3 loop of human 5-HT_{2C} fused to TM6 through the end of the cytoplasmic tail of human 5-HT_{2A}. PCR was performed using pfuTM polymerase (Stratagene) with the buffer system provided by the manufacturer, and 10% DMSO, 0.25 mM of each primer, and 0.5 mM of each of the four (4) nucleotides. The cycle conditions were 25 cycles of 94°C for 1 minute, 57°C (1st round PCR) or 60°C (2nd round PCR) for 1 minute, and 72°C for 1 minute (1st round PCR) or 90 seconds (2nd round PCR).

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[0107] To generate a PCR fragment containing a fusion junction between the human 5-HT_{2A} TM5 and the IC3 loop of 5-HT_{2C}, four (4) primers were used. The two external primers, derived from human 5-HT_{2A}, had the following sequences:

5'-CGTGTCTCTCCTTACTTCA-3' (SEQ.ID.NO.:12)

5 [0108] The other primer used was SEQ.ID.NO.:6 (see note above regarding SEQ.ID.NOS.:6 and 11). The first internal primer utilized was an antisense strand containing the initial 13 bp of IC3 of 5-HT_{2C} followed by the terminal 23 bp derived from TM5 of 5-HT_{2A}:

5'-TCGGCGCAGTACTTTGATAGTTAGAAAGTAGGTGAT-3' (SEQ.ID.NO.:13)

[0109] The second internal primer was a sense strand containing the terminal 14 bp derived from TM5 of 5-HT_{2A} followed by the initial 24 bp derived from IC3 of 5-HT_{2C}:

5'-TTCTAACTATCAAAGTACTGCGCCGACAAGCTTTGATG-3' (SEQ.ID.NO.:14).

[0110] PCR was performed using endogenous human 5-HT_{2A} and a co-template, Fragment C, in a 50 ml reaction volume containing 1X pfu buffer, 10% DMSO, 0.5 mM of each of the four (4) nucleotides, 0.25 mM of each external primer (SEQ.ID.NOS.:11 and 12), 0.06 mM of each internal primer (SEQ.ID.NOS.:13 and 14) and 1.9 units of pfu polymerase (Stratagene). The cycle conditions were 25 cycles of 94°C for 1 minute, 52°C for 1 minute, and 72 °C for 2 minutes and 10 seconds. The 1.3 kb PCR product was then gel purified and digested with Pst I and Eco RI. The resulting 1 kb PstI-Eco RI fragment was used to replace the corresponding fragment in the endogenous human 5-HT_{2A} sequence to generate the mutant 5-HT_{2A} sequence encoding the IC3 loop of 5-HT_{2C}.

20 (b) Replacement of the cytoplasmic tail

[0111] To replace the cytoplasmic tail of 5-HT_{2A} with that of 5-HT_{2C}, PCR was performed using a sense primer containing the C-terminal 22 bp of TM7 of endogenous human 5-HT_{2A} followed by the initial 21 bp of the cytoplasmic tail of endogenous human 5-HT_{2C}:

5'-TTCAGCAGTCAACCCACTAGTCTATACTCTGTTCAACAAAATT-3' (SEQ.ID.NO.:15)

25 The antisense primer was derived from the 3' untranslated region of endogenous human 5-HT_{2C}:

5'-ATTTCTAGACATATGTAGCTTGTACCGT-3' (SEQ.ID.NO.:16).

[0112] The resulting PCR fragment, Fragment D, contained the last 22 bp of endogenous human 5-HT_{2A} TM7 fused to the cytoplasmic tail of endogenous human 5-HT_{2C}. Second round PCR was performed using Fragment D and the co-template was endogenous human 5-HT_{2A} that was previously digested with Acc I to avoid undesired amplification. The antisense primer used was SEQ.ID.NO.:16 (the sequences for SEQ.ID.NOS.:16 and 2 are the same) and the sense primer used was derived from endogenous human 5-HT_{2A}:

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5'-ATCACCTACTTTCTAACTA-3' (SEQ.ID.NO.:17).

[0113] PCR conditions were as set forth in Example 1B3(a) for the first round PCR, except that the annealing temperature was 48 °C and the extension time was 90 seconds. The resulting 710 bp PCR product was digested with Apa I and Xba I and used to replace the corresponding Apa I-Xba I
 5 fragment of either (a) endogenous human 5-HT_{2A}, or (b) 5-HT_{2A} with 2C IC3 to generate (a) endogenous human 5-HT_{2A} with endogenous human 5-HT_{2C} cytoplasmic tail and (b) AP-3, respectively.

4. AP-4 cDNA

[0114] This mutant was created by replacement of the region of endogenous human 5-HT_{2A} from amino acid 247, the middle of TM5 right after Pro²⁴⁶, to amino acid 337, the middle of TM6 just before Pro³³⁸, by the corresponding region of AP-1 cDNA. For convenience, the junction in TM5 is referred to as the "2A-2C junction," and the junction in TM6 is referred to as the "2C-2A junction."

[0115] Three PCR fragments containing the desired hybrid junctions were generated. The 5' fragment of 561 bp containing the 2A-2C junction in TM5 was generated by PCR using endogenous
 15 human 5-HT_{2A} as template, SEQ.ID.NO.:12 as the sense primer, and the antisense primer was derived from 13 bp of 5-HT_{2C} followed by 20 bp of 5-HT_{2A} sequence:

5'-CCATAATCGTCAGGGGAATGAAAAATGACACAA-3' (SEQ.ID.NO.:18)

[0116] The middle fragment of the 323 bp contains endogenous human 5-HT_{2C} sequence derived from the middle of TM5 to the middle of TM6, flanked by 13 bp of 5-HT_{2A} sequences from
 20 the 2A-2C junction and the 2C-2A junction. This middle fragment was generated by using AP-1 cDNA as a template, a sense primer containing 13 bp of 5-HT_{2A} followed by 20 bp of 5-HT_{2C} sequences across the 2A-2C junction and having the sequence:

5'-ATTTTTCATTCCCCTGACGATTATGGTGATTAC-3' (SEQ.ID.NO.:19);

and an antisense primer containing 13 bp of 5-HT_{2A} followed by 20 bp of 5-HT_{2C} sequences across the
 25 2C-2A junction and having the sequence:

5'-TGATGAAGAAAGGGCACCACATGATCAGAAACA-3' (SEQ.ID.NO.:20).

The 3' fragment of 487 bp containing the 2C-2A junction was generated by PCR using endogenous human 5-HT_{2A} as a template and a sense primer having the following sequence from the 2C-2A junction:

30 5'-GATCATGTGGTGCCCTTTCTTCATCACAAACAT-3' (SEQ.ID.NO.:21)

and the antisense primer was SEQ.ID.NO.:6 (see note above regarding SEQ.ID.NOS.:6 and 11).

[0117] Two second round PCR reactions were performed separately to link the 5' and middle fragment (5'M PCR) and the middle and 3' fragment (M3' PCR). The 5'M PCR co-template used

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was the 5' and middle PCR fragment as described above, the sense primer was SEQ.ID.NO.:12 and the antisense primer was SEQ.ID.NO.:20. The 5'M PCR procedure resulted in an 857 bp PCR fragment.

[0118] The M3' PCR used the middle and M3' PCR fragment described above as the co-
5 template, SEQ.ID.NO.:19 as the sense primer and SEQ.ID.NO.:6 (see note above regarding
SEQ.ID.NOS.:6 and 11) as the antisense primer, and generated a 784 bp amplification product. The
final round of PCR was performed using the 857 bp and 784 bp fragments from the second round
PCR as the co-template, and SEQ.ID.NO.:12 and SEQ.ID.NO.:6 (see note above regarding
SEQ.ID.NOS.:6 and 11) as the sense and the antisense primer, respectively. The 1.32 kb
10 amplification product from the final round of PCR was digested with Pst I and Eco RI. Then resulting
1 kb Pst I-Eco RI fragment was used to replace the corresponding fragment of the endogenous human
5-HT_{2A} to generate mutant 5-HT_{2A} with 5-HT_{2C}: C310K/IC3. The Apa I-Xba fragment of AP3 was
used to replace the corresponding fragment in mutant 5-HT_{2A} with 5-HT_{2C}: C310K/IC3 to generate
AP4.

15

EXAMPLE 2

RECEPTOR EXPRESSION

A. pCMV

[0119] Although a variety of expression vectors are available to those in the art, for purposes
20 of utilization for both the endogenous and non-endogenous receptors discussed herein, it is most
preferred that the vector utilized be pCMV. This vector was deposited with the American Type
Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209
USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of
Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and
25 determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC
#203351. See Figure 8.

B. Transfection procedure

[0120] For the generic assay ((³⁵S)GTPγS; Example 3) and the antagonist binding assay
(mesulergine; Example 4), transfection of COS-7 or 293T cells was accomplished using the following
30 protocol.

[0121] On day one, 5x10⁶ COS-7 cells or 1x10⁷ 293T cells per 150mm plate were plated out.
On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube
A was prepared by mixing 20 μg DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.2 ml

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serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120 μ l lipofectamine (Gibco BRL) in 1.2 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45 min. The admixture is referred to as the "transfection mixture". Plated COS-7 cells were washed with 1X PBS, followed by addition of 10 ml serum free DMEM. 2.4 ml of the transfection mixture was then added to the cells, followed by incubation for 4 hrs at 37°C/5% CO₂. The transfection mixture was then removed by aspiration, followed by the addition of 25 ml of DMEM/10% Fetal Bovine Serum. Cells were then incubated at 37°C/5% CO₂. After 72 hr incubation, cells were then harvested and utilized for analysis.

10 EXAMPLE 3

GTP MEMBRANE BINDING SCINTILLATION PROXIMITY ASSAY

[0122] The advantages of using (³⁵S)GTP γ S binding to measure constitutive activation are that: (a) (³⁵S)GTP γ S binding is generically applicable to all G protein-coupled receptors; and (b) (³⁵S)GTP γ S binding is proximal at the membrane surface, thereby making it less likely to pick-up molecules which affect the intracellular cascade. The assay utilizes the ability of G protein-coupled receptors to stimulate (³⁵S)GTP γ S binding to membranes expressing the relevant receptors. Therefore, the assay may be used to directly screen compounds at the disclosed serotonin receptors.

[0123] Figure 9 demonstrates the utility of a scintillation proximity assay to monitor the binding of (³⁵S)GTP γ S to membranes expressing, e.g., the endogenous human 5-HT_{2C} receptor expressed in COS cells. In brief, a preferred protocol for the assay is such that the assay was incubated in 20 mM HEPES, pH 7.4, binding buffer with 0.3 nM (³⁵S)GTP γ S and 12.5 μ g membrane protein and 1 μ M GDP for 30 minutes. Wheatgerm agglutinin beads (25 μ l; Amersham) were then added and the mixture was incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter. As shown in FIG. 9, serotonin, which as the endogenous ligand activates the 5-HT_{2C} receptor, stimulated (³⁵S)GTP γ S binding to the membranes in a concentration dependant manner. The stimulated binding was completely inhibited by 30 μ M mianserin, a compound considered as a classical 5-HT_{2C} antagonist, but also known as a 5-HT_{2C} inverse agonist.

[0124] Although this assay measures agonist-induced binding of (³⁵S)GTP γ S to membranes and can be routinely used to measure constitutive activity of receptors, the present cost of wheatgerm agglutinin beads may be prohibitive. A less costly but equally applicable alternative also meets the needs of large-scale screening. Flash plates and WallacTM scintistrips may be used to format a high throughput (³⁵S)GTP γ S binding assay. This technique allows one to monitor the tritiated ligand

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binding to the receptor while simultaneously monitoring the efficacy via (^{35}S)GTP γ S binding. This is possible because the WallacTM beta counter can switch energy windows to analyze both tritium and ^{35}S -labeled probes.

[0125] Also, this assay may be used for detecting of other types of membrane activation events that result in receptor activation. For example, the assay may be used to monitor ^{32}P phosphorylation of a variety of receptors (including G protein-coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound (^{35}S)GTP γ S or the ^{32}P -phosphorylated receptor will activate the scintillant coated on the wells. Use of Scinti[®] strips (WallacTM) demonstrate this principle. Additionally, this assay may be used for measuring ligand binding to receptors using radiolabeled ligands. In a similar manner, the radiolabeled bound ligand is centrifuged to the bottom of the well and activates the scintillant. The (^{35}S)GTP γ S assay results parallel the results obtained in traditional second messenger assays of receptors.

[0126] As shown in Figure 10, serotonin stimulates the binding of (^{35}S)GTP γ S to the endogenous human 5-HT_{2C} receptor, while mianserin inhibits this response; furthermore, mianserin acts as a partial inverse agonist by inhibiting the basal constitutive binding of (^{35}S)GTP γ S to membranes expressing the endogenous human 5-HT_{2C} receptor. As expected, there is no agonist response in the absence of GDP since there is no GDP present to exchange for (^{35}S)GTP γ S. Not only does this assay system demonstrate the response of the native 5-HT_{2C} receptor, but it also measures the constitutive activation of other receptors.

[0127] Figure 11A and Figure 11B demonstrate the enhanced binding of (^{35}S)GTP γ S to membranes prepared from 293T cells expressing the control vector alone, the native human 5-HT_{2C} receptor or the AP-1 receptor was observed (data not shown). The total protein concentration used in the assay affects the total amount of (^{35}S)GTP γ S binding for each receptor. The c.p.m. differential between the CMV transfected and the constitutively active mutant receptor increased from approximately 1000 c.p.m at 10 μg /well to approximately 6-8000 c.p.m. at 75 μg /well protein concentration, as shown in Figure 11.

[0128] The AP-1 receptor showed the highest level of constitutive activation followed by the wild type receptor, which also showed enhanced (^{35}S)GTP γ S binding above basal. This is consistent with the ability of the endogenous human 5-HT_{2C} receptor to accumulate intracellular IP₃ in the absence of 5-HT stimulation (Example 5) and is also consistent with published data claiming that the endogenous human 5-HT_{2C} receptor has a high natural basal activity. Therefore, the AP-1 receptor

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demonstrates that constitutive activity may be measured by proximal (^{35}S)GTP γ S binding events at the membrane interface.

EXAMPLE 4

SEROTONIN RECEPTOR AGONIST/ANTAGONIST

5 COMPETITIVE BINDING ASSAY

[0129] Membranes were prepared from transfected COS-7 cells (*see* Example 2) by homogenization in 20 mM HEPES and 10 mM EDTA, pH 7.4 and centrifuged at 49,000 x g for 15 min. The pellet was resuspended in 20 mM HEPES and 0.1 mM EDTA, pH 7.4, homogenized for 10 sec. using a Polytron homogenizer (Brinkman) at 5000 rpm and centrifuged at 49,000 x g for 15 min.
10 The final pellet was resuspended in 20 mM HEPES and 10 mM MgCl_2 , pH 7.4, homogenized for 10 sec. using polytron homogenizer (Brinkman) at 5000 rpm.

[0130] Assays were performed in triplicate 200 μl volumes in 96 well plates. Assay buffer (20 mM HEPES and 10 mM MgCl_2 , pH 7.4) was used to dilute membranes, ^3H -LSD, ^3H -mesulergine, serotonin (used to define non-specific for LSD binding) and mianserin (used to define non-specific for
15 mesulergine binding). Final assay concentrations consisted of 1 nM ^3H -LSD or 1 nM ^3H -mesulergine, 50 μg membrane protein and 100 μM serotonin or mianserin. LSD assays were incubated for 1 hr at 37° C, while mesulergine assays were incubated for 1 hr at room temperature. Assays were terminated by rapid filtration onto Wallac Filtermat Type B with ice cold binding buffer using Skatron cell harvester. The radioactivity was determined in a Wallac 1205 BetaPlate counter.

20 EXAMPLE 5

INTRACELLULAR IP_3 ACCUMULATION ASSAY

[0131] For the IP_3 accumulation assay, a transfection protocol different from the protocol set forth in Example 2 was utilized. In the following example, the protocols used for days 1-3 were slightly different for the data generated for Figures 12 and 14 and for Figures 13 and 15; the protocol
25 for day 4 was the same for all conditions.

A. COS-7 and 293 Cells

[0132] On day one, COS-7 cells or 293 cells were plated onto 24 well plates, usually 1×10^5 cells/well or 2×10^5 cells/well, respectively. On day two, the cells were transfected by first mixing 0.25 μg DNA (*see* Example 2) in 50 μl serum-free DMEM/well and then 2 μl lipofectamine in 50 μl
30 serum-free DMEM/well. The solutions ("transfection media") were gently mixed and incubated for 15-30 minutes at room temperature. The cells were washed with 0.5 ml PBS and then 400 μl of serum free media was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37°C/5% CO_2 . Then the transfection media was removed and replaced with

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1ml/well of regular growth media. On day 3, the media was removed and the cells were washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum-free media (GIBCO BRL) was added to each well with 0.25 μ Ci of 3 H-myo-inositol/well and the cells were incubated for 16-18 hours overnight at 37°C/5% CO₂. Protocol A.

5 **B. 293 Cells**

[0133] On day one, 1×10^7 293 cells per 150 mm plate were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 μ g DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.2 ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 120 μ l lipofectamine
10 (Gibco BRL) in 1.2 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30-45 min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4 ml of the transfection mixture was then added to the cells, followed by incubation for 4 hrs at 37°C/5% CO₂. On day 3, cells were trypsinized and counted, followed by
15 plating of 1×10^6 cells/well (poly D-lysine treated 12-well plates). Cells were permitted to adhere to the wells, followed by one wash with 1XPBS. Thereafter, 0.5 μ Ci 3 H-inositol in 1ml inositol-free DMEM was added per well. Protocol B.

[0134] On day 4, the cells were washed with 0.5 ml PBS and then 0.45 ml of assay medium was added containing inositol-free/serum free media, 10 μ M pargyline, 10 mM lithium chloride, or
20 0.4 ml of assay medium and 50 μ l of 10x ketanserin (ket) to a final concentration of 10 μ M. The cells were then incubated for 30 minutes at 37° C. Then the cells were washed with 0.5 ml PBS and 200 μ l of fresh/ice cold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) was added/well. The solution was kept on ice for 5-10 minutes or until the cells were lysed and then neutralized by 200 μ l of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate was then transferred into 1.5 ml micro-
25 centrifuge tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 seconds and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100-200 mesh). The resin was washed with water and 0.9 ml of the upper phase was loaded onto the column. The column was washed with 10 ml of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol trisphosphates were eluted into scintillation vials containing 10 ml of
30 scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H₂O and stored at room temperature in water. Results are discussed below.

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[0135] Figure 12 is an illustration of IP3 production from the human 5-HT_{2A} receptor which was mutated using the same point mutation as set forth in Casey, which rendered the rat receptor constitutively active. The results represented in Figure 12, support the position that when the point mutation shown to activate the rat receptor is introduced into the human receptor, little activation of the receptor is obtained that would allow for appropriate screening of candidate compounds, with the response being only moderately above that of the endogenous human 5-HT_{2A} receptor. Generally, a response of at least 2X above that of the endogenous response is preferred.

[0136] Figure 13 provides an illustration comparing IP3 production from endogenous 5-HT_{2A} receptor and the AP4 mutation. The results illustrated in Figure 13 support the position that when the novel mutation disclosed herein is utilized, a robust response of constitutive IP3 accumulation is obtained (e.g., over 2X that of the endogenous receptor).

[0137] Figure 14 provides an illustration of IP3 production from AP3. The results illustrated in Figure 14 support the position that when the novel mutation disclosed herein is utilized, a robust response of constitutive IP3 accumulation is obtained.

[0138] Figure 15 provides bar-graph comparisons of IP3 accumulation between endogenous human 5-HT_{2C} receptor and AP-1. Note that the endogenous receptor has a high degree of natural constitutive activity relative to the control CMV transfected cells (i.e., the endogenous receptor appears to be constitutively activated).

Example 6

Screening of Compounds Known to Have 5-HT_{2C} Antagonist Activity Against Non-Endogenous, Constitutively Activated Human Serotonin Receptor: AP-1

[0139] A final concentration of 12.5 µg membranes prepared from COS7 cells (see Example 2) transiently expressing constitutively active mutant human 5-HT_{2C} receptor AP-1 were incubated with binding buffer (20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM MgCl₂ · 6H₂O, 0.2% saponin, and 0.2 mM ascorbate), GDP (1 µM) and compound in a 96-well plate format for a period of 60 minutes at ambient room temperature. Plates were then centrifuged at 4,000 rpm for 15 minutes followed by aspiration of the reaction mixture and counting for 1 minute in a Wallac™ MicroBeta plate scintillation counter. A series of compounds known to possess reported 5-HT_{2C} antagonist activity were determined to be active in the (³⁵S)GTPγS binding assay using AP-1. IC₅₀ determinations were made for these commercially available compounds (RBI, Natick, Mass.). Results are summarized in TABLE 3. For each determination, eight concentrations of test compounds were tested in triplicate.

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The negative control in these experiments consisted of AP-1 receptor without test compound addition, and the positive control consisted of 12.5 $\mu\text{g}/\text{well}$ of COS7 cell membranes expressing the CMV promoter without expressed AP-1 receptor.

TABLE 3

Test Compound	Known Pharmacology	IC ₅₀ (nM) in GTP- γ -(³⁵ S) Assay
Metergoline	5-HT ₂ /IC antagonist	32.0
Mesulergine	5-HT ₂ /IC antagonist	21.2
Methysergide	5-HT ₂ /IC antagonist	6.1
Methiothepin	5-HT ₁ antagonist	20.4
Normethylclozapin	5-HT ₂ /IC antagonist	21.4
Fluoxetine	5-HT reuptake inhibitor	114.0
Ritanserlin	5-HT ₂ /IC antagonist	19.4

- 5 The IC₅₀ results confirm that the seven tested compounds showed antagonist activity at the AP-1 receptor.

EXAMPLE 7

10 SCREENING OF CANDIDATE COMPOUNDS AGAINST NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN SEROTONIN RECEPTORS: AP-1

- 15 [0140] Approximately 5,500 candidate compounds (Tripos, Inc., St. Louis, MO) were screened using the assay protocol of Example 3 (with AP-1 mutant receptor) for identification as inverse agonists against the receptor; for this assay, an arbitrary cut-off of at least 50% inhibition was established for identification of inverse agonists. Approximately 120 of these compounds evidenced at least 50% inhibition of (³⁵S) GTP γ S binding at 10 μM candidate compound (data not shown).

EXAMPLE 8

- 20 [0141] The candidate compounds identified from Example 7 were then screened using the assay protocol of Example 4 (mesulergine), using the AP-1 mutant receptor. IC₅₀ (nM) values were determined; five of the nearly 120 compounds of Example 7 were determined to have potent binding affinity for the receptor. Results are summarized in TABLE 4.

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TABLE 4

Candidate Compound	IC ₅₀ (nM) in Mesulergine Assay
Compound 3	205.0
Compound 4	46.5
Compound 5	209.0
Compound 6	147.0
Compound 7	1,810.0

EXAMPLE 9A

GENERAL SCREENING PARADIGM: SELECTION OF PRE-CLINICAL CANDIDATE

5 LEADS

[0142] The "primary" screen designed to directly identify human 5-HT_{2A}/5-HT_{2C} receptor inverse agonists consisted of a membrane-based GTPγS binding assay utilizing membranes prepared from COS7 cells transiently transfected with AP-1 human receptor. Candidate compounds (10μM final assay concentration) directly identified as inhibiting receptor-mediated increases in GTPγS binding by greater than 50-75% (arbitrary cut-off value) were considered active "hits". Primary assay hits were then re-tested in the same assay to reconfirm their inverse agonist activity. If primary assay hits were reconfirmed active (50% or greater inhibition), and therefore directly identified as, *e.g.*, an inverse agonist, one of two approaches were available: (a) so-called "directed libraries" could be created, *i.e.*, additional candidate compounds were synthesized based upon the structures of the reconfirmed hits (geared towards, *e.g.*, improvement in the characteristics of the compounds) whereby the directed library compounds were then evaluated for the ability to compete for radioligand binding to both mutant 5-HT_{2C} (AP-1) and endogenous 5-HT_{2A} receptors, or (b) the reconfirmed hits were then evaluated for the ability to compete for radioligand binding to both mutant 5-HT_{2C} (AP-1) and endogenous 5-HT_{2A} receptors. Thus, when approach (a) was used, because these directed library candidate compounds were based upon the structures of compounds that were directly identified from the membrane-based GTPγS binding assay, the directed library compounds were not re-tested in the membrane-based GTPγS binding assay but rather were then confirmed via the radioligand binding analysis. The radioligand binding analysis tests were initially performed at 10μM test compound in triplicate and if the compound inhibited radiolabeled binding by 50% or more, the analysis was followed by eight concentration competition curves to determine K_i values. The last step in secondary assay evaluation was to determine if test compounds were capable of inhibiting AP-3 receptor-

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mediated accumulation of inositol phosphates (e.g., IP₃). This final assay confirms that the directly identified compounds retained inverse agonist properties.

Example 9B

5 **CONSTITUTIVELY ACTIVATED HUMAN 5-HT_{2C} RECEPTOR (AP-1)**
MEDIATED FACILITATION OF GTPγS BINDING TO COS7 MEMBRANES

[0143] This protocol is substantially the same as set forth above in Example 6. Primary screening assays measuring GTPγS binding to membranes prepared from COS7 cells transiently transfected with human mutated 5-HT_{2C} receptor (AP-1) were used to directly identify inverse agonists in screening libraries (Tripos, Inc.). Candidate compound screens were performed in a total assay volume of 200 μl using scintillant-coated Wallac Scintistrip™ plates. The primary assay was comprised of the following chemicals (at indicated final assay concentrations): 20 mM HEPES, pH 7.4, 100 mM NaCl, 20 mM MgCl₂, 0.2% saponin, 0.2 mM ascorbic acid, 1 μM GDP, 0.3 nM GTPγ³⁵S, and 12.5 μg of the above defined membranes. Incubations were performed for 60 minutes at ambient room temperature. The binding assay incubation was terminated by centrifugation of assay plates at 4,000 rpm for 15 minutes, followed by rapid aspiration of the reaction mixture and counting in a Wallac MicroBeta™ scintillation counter.

[0144] Primary screening of candidate compounds initially involved testing of 72 test compounds per assay plate (96-well plates were utilized), at a final assay concentration of 10 μM candidate compound, in single replicates. A total of sixteen wells of each plate were dedicated for an eight concentration clozapine (a confirmed 5-HT_{2C/2A} inverse agonist) dose response curve (duplicate determinations at each concentration). Finally, a total of five assay wells of each plate were dedicated to define the negative control (AP-1 receptor expressing membranes without addition of candidate compounds) and three wells from each plate to define the positive control (membranes without AP-1 receptor).

[0145] Reconfirmation experiments involve re-testing candidate compounds in the same assay described above, except that candidate compounds were evaluated in triplicate, thus allowing evaluation of 24 compounds per 96-well assay plate. Similar to the primary assay plates, an eight concentration clozapine dose response curve (duplicate determinations at each concentration) and the same negative and positive control wells were also included within each 96-well plate.

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Example 9C(1)**COMPETITION STUDIES FOR DIRECTLY IDENTIFIED COMPOUNDS:****MUTATED HUMAN 5-HT_{2C} RECEPTOR (AP-1)**

[0146] Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients consisted of assay buffer (20 mM HEPES and 10 mM MgCl₂), 1nM (³H) mesulergine, and 50 µg of membranes (COS7 with AP-1 as defined above). Nonspecific (³H) mesulergine binding was defined in the presence of 100 µM mianserin. Incubations were performed for 1 hour at 37°C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (each containing 100 µM mianserin). For one concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM, in triplicate. For IC₅₀ determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated, in triplicate. A total of 16 wells were designated for an eight concentration mianserin dose response curve evaluation for both assays.

EXAMPLE 9C(2)**COMPETITION STUDIES WILD TYPE HUMAN 5-HT_{2A} RECEPTOR**

[0147] Radioligand binding competition experiments were performed in a total assay volume of 200 µl using standard 96-well microtiter plates. The final assay ingredients comprised assay buffer (20 mM HEPES and 10mM MgCl₂), 1nM (³H)LSD, and 50 µg of the above-defined membranes (COS7 with AP-1). Nonspecific (³H)LSD binding was defined in the presence of 100 µM serotonin. Incubations were performed for 1 hour at 37° C. Receptor bound radioligand was resolved from free radioligand by rapid filtration of the assay mixture over a Wallac Filtermat™ Type B filter, followed by washing with ice-cold assay buffer using a Skatron™ cell harvester. Radioactivity was counted using a Wallac 1205 BetaPlate™ counter. Each assay plate contained five negative control wells (membranes expressing receptor and no candidate compound addition) and three positive control wells (containing 100 µM mianserin). For one concentration tests, candidate compounds were diluted into assay buffer and screened at a final concentration of 10 µM in triplicate. For IC₅₀ determinations, candidate compounds were diluted in assay buffer and eight different concentrations were evaluated in triplicate. A total of 16 wells were designated for an eight concentration serotonin dose response curve evaluation for both assays.

EXAMPLE 9D**RECEPTOR-MEDIATED INOSITOL PHOSPHATE ACCUMULATION**

[0148] Candidate compound identified in the assays of Examples 9A-9C were then evaluated for inositol phosphate accumulation, following the protocol of Example 5 (COS7 cells expressing human mutated 5-HT_{2A} receptor, AP-3), modified as follows: tube A was prepared by mixing 16 µg DNA (e.g., pCMV vector; pCMV vector AP-1 cDNA, etc.) in 1.0 ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was prepared by mixing 60 µl lipofectamine (Gibco BRL) in 1.0 ml serum free DMEM. Tubes A and B were then admixed by inversions (several times), followed by incubation at room temperature for 30 min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 10 ml Serum Free DMEM, followed by addition of 11 ml Serum Free DMEM. 2.0 ml of the transfection mixture was then added to the cells, followed by incubation for 5 hrs at 37° C/5% CO₂. On day 3, cells were trypsinized and counted, followed by plating of 1x10⁶ cells/well (12-well plates). Cells were permitted to adhere to the wells for 8 hrs, followed by one wash with 1xPBS. Thereafter, 0.5 µCi ³H-inositol in 1ml inositol-free DMEM was added per well.

[0149] On day 4, the cells were washed with 1.5 ml PBS and then 0.9 ml of assay medium was added containing inositol-free/serum free media, 10 µM pargyline, 10 mM lithium chloride, for 5min in 37°C/5% CO₂ followed by 100µl addition of candidate compound diluted in the same material. The cells were then incubated for 120 minutes at 37° C. Then the cells were washed with 1.5 ml PBS and 200 µl of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) was added/well. The solution was kept on ice for 5-10 minutes or until the cells were lysed and then neutralized by 200 µl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate was then transferred into 1.5 ml micro-centrifuge tubes and 1 ml of chloroform/methanol (1:2) was added/tube. The solution was vortexed for 15 seconds and the upper phase was applied to a Biorad AG1-X8 anion exchange resin (100-200 mesh). The resin was washed with water and 0.9 ml of the upper phase was loaded onto the column. The column was washed with 10 ml of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol trisphosphates were eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns were regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with ddH₂O and stored at room temperature in water.

[0150] Following this round of assaying, candidate compounds having an IC₅₀ value of less than 10 µM were considered as potential leads for the development of pharmaceutical compositions.

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SCREENING CANDIDATE COMPOUNDS

[0151] Following the protocols set forth above, one compound, Compound 7 (Example 8, *supra*) evidenced the following results as shown in TABLE 4A:

TABLE 4A

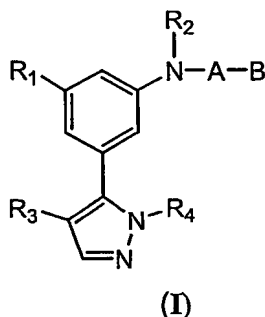
Compd No.	GTPyS AP-1 Percent Inhibition Relative To Positive Control (Primary)	GTPyS AP-1 Percent Inhibition Relative To Positive Control (Reconfirm)	Competitive Binding AP-1 ((³ H)mesulergine) IC ₅₀ Value (nM)	Competitive Binding WT 5-HT _{2A} ((³ H)LSD) IC ₅₀ Value (nM)	Inositol Phosphate Accumulation AP-3 IC ₅₀ Value (nM)
7	-1%	31%	2100 850	46	52 90

5

[0152] Based upon these results, structure activity analysis of the Compound 7 compound suggested that a series of derivatives of 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine would exhibit similar 5-HT_{2A} activity and selectivity. A series of derivatives of 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine were synthesized. These "directed" library compounds (Tripos, Inc.) were then analyzed in accordance with the protocols of Examples 9c(1), 9c(2) and 9d.

10

[0153] This series of compounds exhibits highly selective 5-HT_{2A} activity. Accordingly, in one aspect of the invention, a series of compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors is designated by the general Formula (I):



15 wherein:

i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂,

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OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl;

R₁₀ is H or C₁₋₆ alkyl;

R₇ is H or C₁₋₆ alkyl;

ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

iii) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen,

-C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

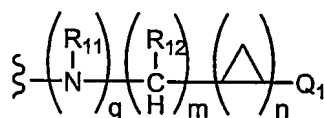
iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO₂;

vi) B is L₁ or L₂;

L₁ is:

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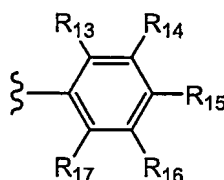
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

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R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

Q₁ is:

wherein:

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R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, halogen, CN, NR₈R₉, COOR₁₀, SR₁₀, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

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L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

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[0154] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle. C₁₋₆ alkyl moieties can be straight chain or branched; optionally substituted C₁₋₆

alkyl moieties can be straight chain or branched; C₂₋₆ alkenyl moieties can be straight chain or branched; and optionally substituted C₂₋₆ alkenyl moieties can be straight chain or branched. Examples of suitable C₁₋₆ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl. Halogens are typically F, Cl, Br, and I. Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxalyl, quinazolinyl and benzothienyl.

5 [0155] In some embodiments of the foregoing Formula (I), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0156] In some embodiments of the foregoing Formula (I), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

15 [0157] In some embodiments of the compounds of Formula (I), B is L₁, q is 1, m is 0, and n is 0. In further embodiments of the compounds of Formula (I), B is L₁, q is 1, m is 1, and n is 0. In further embodiments of the compounds of Formula (I), B is L₁, q is 1, m is 0, and n is 1. In further embodiments of the compounds of Formula (I), B is L₁, q is 0, m is 0, and n is 0.

20 [0158] In some embodiments of the compounds of Formula (I), B is L₂. In further embodiments of the compounds of Formula (I), A, is C(=O). In further embodiments of the compounds of Formula (I), A, is C(=S). In further embodiments of the compounds of Formula (I), A, is SO₂.

[0159] In further embodiments of the compounds of Formula (I), R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃.

25 [0160] In some embodiments of the compounds of Formula (I), R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

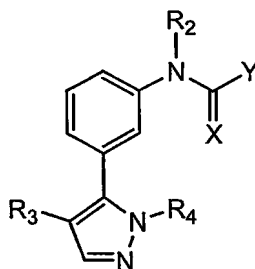
[0161] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 0, n is 0 and A is C(=O), R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃.

- [0162] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 0, n is 0 and A is C(=O), R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 5 [0163] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 1, n is 0 and A is C(=O), R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- [0164] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 1, and n is 0, R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 10 [0165] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 0, n is 1 and A is C(=O), R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 15 [0166] In some embodiments of the compounds of Formula (I), where B is L₁, q is 1, m is 0, and n is 1, R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- [0167] In some of each of the foregoing embodiments of the compounds of Formula (I), R₂ is H and R₄ is methyl of each of the foregoing embodiments of the compounds of Formula (I), R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH₂ or NO₂.
- 20 [0168] In some embodiments of the compounds of Formula (I), where B is L₁, q is 0, m is 0, and n is 0, A is SO₂. In some of such embodiments, R₂ is H and R₄ is methyl. In still further such embodiments, R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 25 [0169] In some embodiments of the compounds of Formula (I), B is L₂. In some such embodiments, A is (C=O). In further such embodiments, R₄ is methyl. In still further such embodiments, R₂ is H. In further such embodiments, Q₁ is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl, butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-
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methoxyphenyl, 2-chlorophenyl, $-C(CH_3)=CH$, 1-(N-pyridyl)ethyl, or 9-fluorenylmethyl. In further such embodiments, R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃; and R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

[0170] In another aspect of the invention, a series of compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors is designated by Formula (A):



(A)

10 wherein:

R₂ is H or lower alkyl(C₁₋₄);

R₃ is lower alkyl (C₁₋₆), or halogen;

R₄ is lower alkyl (C₁₋₆);

X is either Oxygen or Sulfur;

15 Y is NR₁₅R₁₆, or (CH₂)_mR₁₇, or O(CH₂)_nR₁₇;

m=0-4

n=0-4

R₁₅ is H or lower alkyl(C₁₋₄);

20 R₁₆ and R₁₇ are independently C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₁₈R₁₉, NR₁₈R₁₉, NHCOCH₃, OCF₃, SMe, COOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

25 R₁₈ and R₁₉ are independently a H or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃,

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SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

or R₁₈ and R₁₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₂₃, SO₂NR₂₁R₂₂, SO₃R₂₃, NHCOCH₃, COEt, COMe, or halogen;

R₂₀ and R₂₃ are each independently selected from H or C₁₋₆ alkyl;

R₂₁ and R₂₂ are each independently are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₂₀, SO₃R₂₀, COEt, NHCOCH₃, or aryl;

an aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 heteroatoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

C₁₋₆ alkyl moieties can be straight chain or branched;

optionally substituted C₁₋₆ alkyl moieties can be straight chain or branched;

C₂₋₆ alkenyl moieties can be straight chain or branched; and

optionally substituted C₂₋₆ alkenyl moieties can be straight chain or branched.

[0171] Examples of suitable C₁₋₆ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0172] Halogens are typically F, Cl, Br, and I.

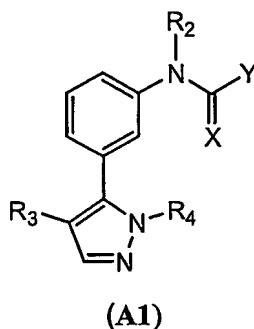
[0173] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothienyl.

[0174] In some embodiments of the foregoing genus (A), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0175] In some embodiments of the foregoing genus (A), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

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[0176] In some preferred embodiments, compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors are designated by the general Formula A1:



5 wherein:

R₃ is F, Cl, Br, I, C₁₋₆ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₆ alkenyl;

X is O or S;

Y is NR₁₅R₁₆, or (CH₂)_mR₁₇, or O(CH₂)_nR₁₇;

10 m is an integer between 0 and 4, inclusive;

n is an integer between 0 and 4, inclusive;

R₄ is H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₈ alkenyl;

15 R₂ and R₁₅ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₈ alkenyl;

R₁₆ and R₁₇ are each independently selected from: C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is
 20 independently selected from: H, F, Cl, Br, I, R₂₀, CF₃, CF₂R₇, CF₂CF₂, CCl₃, CCl₂R₇, CCl₂CCl₂R₇, NR₁₈R₁₉, NR₁₈COR₂₀, NR₁₈SO₂R₂₀, OR₂₀, OCF₃, OCF₂R₂₀, OCF₂CF₂R₂₀, OCOR₂₀, OSO₂R₂₀, OPO(OR₂₀)₂, SR₂₀, SCF₃, SCF₂R₂₀, SCF₂CF₂R₂₀, SCOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, PO(OR₂₀)₃, PO(OR₂₀)₂R₂₀, NO₂, CN, CNR₂₀(NR₁₈R₁₉), CNR₁₈(SR₂₀), COOR₂₀, COSR₂₀, CONR₁₈R₁₉,

25 with the proviso that when R₁₆ or R₁₇ contains an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₂₀ is H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, C₂₋₈ alkenyl, aryl or alkylaryl;

R₁₈ and R₁₉ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is

5 independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

10 with the proviso that when either or both of R₁₈ or R₁₉ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

or

20 R₁₈ or R₁₉ may together form part of a 5, 6 or 7 membered cyclic structure, with said structure being saturated or unsaturated, and further with said structure containing up to four heteroatoms selected from O, N or S, and further wherein each moiety within said cyclic structure being optionally substituted by up to four substituents in any position independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

25 with the proviso that wherein when R₁₈ or R₁₉ form an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together

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be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure.

[0177] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

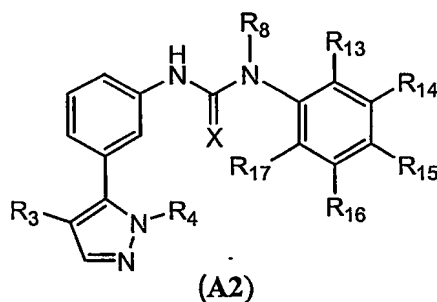
Examples of suitable C₁₋₈ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0178] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl, and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl, and benzothienyl.

[0179] In some embodiments of the foregoing genus (A), compounds of Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0180] In some embodiments of the foregoing genus (A), compounds of Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0181] Preferred compounds falling within the scope of general Formula (A) as Class (1) compounds where Y = N₁₅R₁₆ and has the Formula (A2):



wherein:

X is O or S;

R₄ is H or CH₃;

R₈ and R₂₀ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₈ alkenyl;

R₁₅ is H, F, Cl, Br, I, R₂₀, CF₃, CF₂R₂₀, CF₂CF₂, CCl₃, CCl₂R₂₀, CCl₂CCl₂R₂₀, NR₁₈R₁₉, NR₁₉COR₂₀, NR₁₉SO₂R₂₀, OR₂₀, OCF₃, OCF₂R₂₀, OCF₂CF₂R₂₀, OCOR₂₀, OSO₂R₂₀, OPO(OR₂₀)₂,

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SR₂₀, SCF₃, SCF₂R₂₀, SCF₂CF₂R₂₀, SCOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, PO(OR₂₀)₃, PO(OR₂₀)₂R₂₀, NO₂, CN, CNR₂₀(NR₁₈R₁₉), CNR₁₉(SR₂₀), COOR₂₀, COSR₂₀, CONR₁₈R₁₉,

with the proviso that when a position adjacent to R₁₅ is substituted, then R₁₅ and said adjacent position can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₁₈ and R₁₉ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

with the proviso that when either or both of R₁₈ or R₁₉ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ each independently selected from the following: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

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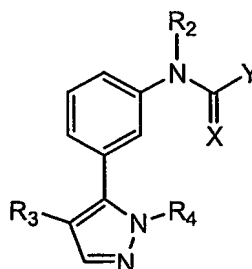
with the proviso that when any two adjacent positions of R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are substituted, said two adjacent positions can together be further selected from SCH_2S , SCH_2CH_2S , OCH_2O , or OCH_2CH_2O to form a bi-cyclic structure; and with the proviso that at least one of R_{13} , R_{14} , R_{15} , R_{16} and R_{17} must be H.

5

[0182] In some embodiments of the foregoing genus (A), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0183] In some embodiments of the foregoing genus (A), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

10 [0184] A more preferred series of compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors is designated by the general Formula (B):



(B)

wherein:

- 15 R_2 is H or lower alkyl (C_{1-4});
 R_3 is Me, or Et, or halogen;
 X is either Oxygen or Sulfur;
 Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;
 R_4 is lower alkyl (C_{1-6});
 20 $m=0-4$
 $n=0-4$

R_{15} is H or lower alkyl(C_{1-4});

- R_{16} and R_{17} are independently C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl group and each said group may be optionally substituted by up to four substituents in any position
 25 independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{20}$, SO_3R_{20} , $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy

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wherein each of the C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, aryl and aryloxy groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

R₁₈ and R₁₉ are independently a H or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl

or R₁₈ and R₁₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₇, SO₂NR₂₄R₂₅, SO₃R₂₆, NHCOCH₃, COEt, COMe, or halogen;

R₂₀ and R₂₃ are each independently selected from H or C₁₋₆ alkyl;

R₂₁ and R₂₂ are each independently are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₂₀, SO₃R₂₀, COEt, NHCOCH₃, or aryl;

C₁₋₆ alkyl moieties can be straight chain or branched;

optionally substituted C₁₋₆ alkyl moieties can be straight chain or branched:

C₂₋₆ alkenyl moieties can be straight chain or branched; and

optionally substituted C₂₋₆ alkenyl moieties can be straight chain or branched.

[0185] Examples of suitable C₁₋₆ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0186] Halogens are typically F, Cl, Br, and I.

[0187] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl, thiazolyl and isothiazoyl. Examples of polycycle moieties include, but are not restricted to, naphthyl,

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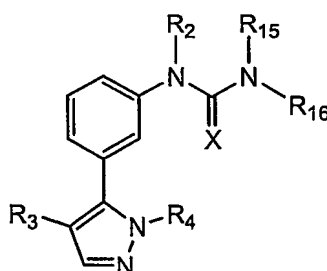
benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothienyl.

[0188] In some embodiments of the foregoing genus (B), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

5 [0189] In some embodiments of the foregoing genus (B), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0190] Exemplary compounds of general Formula (A), Class (1) are set forth below. Based upon *in vivo* data developed (as set forth below), Compounds 8 and 9 are particularly preferred.

[0191] A first series of compounds having 5-HT_{2A} receptor activity is represented by a class
10 (I) of compounds of Formula (B) wherein Y=NR₁₅R₁₆ and is Formula (B1):



(B1)

wherein:

Preferably R₂ and R₁₅ are H;

Preferably R₃ is Br;

15 Preferably X is O;

Preferably R₄ is Me.

In some embodiments of the foregoing genus (B), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

20 [0192] In some embodiments of the foregoing genus (B), class (1), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

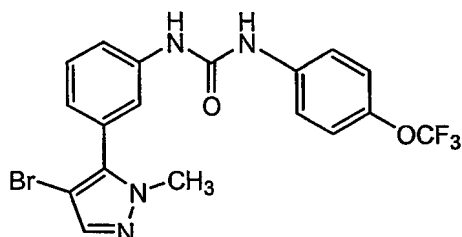
[0193] In reference to Formula (B1) R₁₆ is preferably 4-trifluoromethoxyphenyl, 4-trifluoromethoxybenzyl, 4-chlorophenyl or 4-fluorophenyl.

[0194] Certain preferred compounds are:

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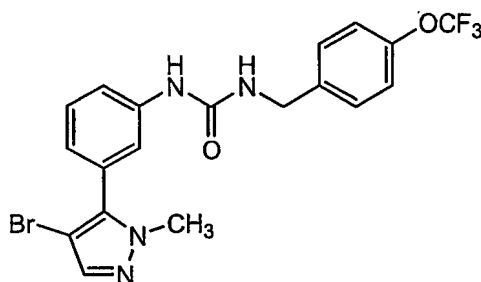
Compound 7

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl)aminocarboxamide



5

Compound 10

N-(3-(4-bromo-2-methylpyrazol-3-yl)-phenyl)((4-trifluoromethoxy)phenylmethyl)
Aminocarboxamide

10

[0195] These two compounds demonstrated the following activities using the assay protocols defined in the Examples above:

15

TABLE 5

Compound Number	Competitive Binding AP-1 ((³ H)mesulergine) IC ₅₀ Value (μM)	Competitive Binding WT 5-HT _{2A} ((³ H)LSD) IC ₅₀ Value (μM)	Inositol Phosphate Accumulation AP-3 IC ₅₀ Value (μM)
Compound 7	2.1	.046	.052
Compound 10	1.2	.45	.0171

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[0196] Additional compounds are set forth below. Inositol phosphate accumulation assays evidence the activity of test compounds. Both single concentration percentages of control values and IC_{50} determinations indicate activity. In the tables below the column legends have the following meanings:

5 IP₃ % Control: The values in this column reflect an IP Accumulation Assay where the test compounds were evaluated at one concentration of 10 μ M. For these assays, the compound was diluted into inositol-free Dulbecco's Eagle Media containing 10 μ M pargyline and 10 mM LiCl and tested at a final assay concentration of 10 μ M, in triplicate. The percent control value was calculated based on the control in which no test compound was added.

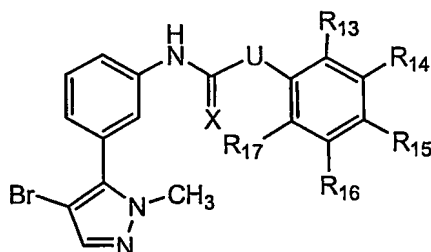
10 IP₃ AP-3 IC₅₀ nM: The values in this column reflect an IP accumulation assay in which the test compound was evaluated at several different concentrations whereby an IC_{50} could be determined. This column corresponds to the column appearing in the tables above which is labeled: Inositol Phosphate Accumulation, AP-3, IC_{50} Value (μ M).

15 WT 5-HT_{2A} LSD IC₅₀ nM: The values in this column reflect a competitive binding assay using LSD. This column corresponds to the column appearing in the tables above which is labeled: Competitive Binding, WT 5-HT_{2A}, ((³H)LSD), IC_{50} Value (μ M).

[0197] Compounds listed in each of the following tables reference the structures immediately preceding the table. A "dash" in the table indicates that no value was determined.

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TABLE 6



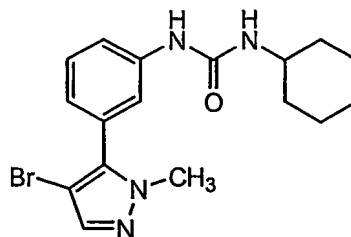
Compound Name									
Compound No.	R ₁₅	R ₁₄	R ₁₃	R ₁₆	X	U	IP ₃ % of Control	IP ₃ AP-3 IC ₅₀ nM	WT 5-HT _{2A} LSD IC ₅₀ nM
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino)carboxamide									
Compound 11	SCH ₃	H	H	H	O	NH	16	17	4
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino)carboxamide									
Compound 8	Cl	H	H	H	O	NH	10	3.2	11
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-fluorophenyl)carboxamide									
Compound 9	F	H	H	H	O	NH	11	-	7
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide									
Compound 12	H	H	CF ₃ O	H	O	NH	11	-	200
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-nitrophenyl)carboxamide									
Compound 13	H	H	NO ₂	H	O	NH	27	-	238
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-methoxyphenyl)carboxamide									
Compound 14	MeO	H	H	H	O	NH	12	-	19

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl)carboxamide									
Compound 15	H	H	Me	H	O	NH	32	-	131
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-(trifluoromethyl)phenyl)carboxamide									
Compound 16	CF ₃	H	H	H	O	NH	11	-	65
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-chlorophenyl)carboxamide									
Compound 17	H	Cl	H	H	O	NH	11	-	39
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-chlorophenyl)carboxamide									
Compound 18	H	H	Cl	H	O	NH	6	-	249
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)phenyl)carboxamide									
Compound 19	isopropyl	H	H	H	O	NH	7	-	338
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-methoxyphenyl)carboxamide									
Compound 20	H	MeO	H	H	O	NH	7	-	106
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(3-methylphenyl)carboxamide									
Compound 21	H	Me	H	H	O	NH	14	-	57
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)carboxamide									
Compound 22	CF ₃ O	H	H	H	O	NCH ₃	-	193	2
N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound 23	t-butyl	H	H	H	O	NH	17	-	476
N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound 24	NMe ₂	H	H	H	O	NH	9	-	309

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N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide									
Compound 25	Me	Cl	H	Cl	O	NH	23	-	122
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-(trifluoromethylthio)phenyl)carboxamide									
Compound 26	CF ₃ S	H	H	H	O	NH	12	-	56
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-fluorophenyl)carboxamide									
Compound 27	H	H	F	H	O	NH	12	-	37
2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino)benzamide									
Compound 27	H	H	CONH ₂	H	O	NH	31	-	7473
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(4-cyanophenyl)carboxamide									
Compound 29	CN	H	H	H	O	NH	12	-	2
((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)-N-(2-cyanophenyl)carboxamide									
Compound 30	H	H	CN	H	O	NH	30	-	348

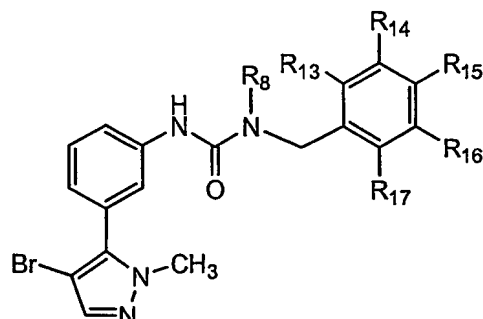
TABLE 7



Compound No.	N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(cyclohexylamino)carboxamide	IP ₃ AP-3	WT 5-HT _{2A} LSD
		IC ₅₀ nM	IC ₅₀ nM
Compound 31		114	81

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TABLE 8



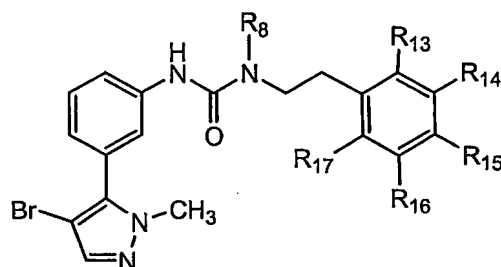
Compound Name							
Compound No.	R ₁₅	R ₁₄	R ₁₃	R ₁₆	R ₈	IP ₃ AP-3 IC ₅₀ nM	WT 5-HT _{2A} LSD IC ₅₀ nM
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(phenylmethylamino)carboxamide							
Compound 32	H	H	H	H	H	120	47
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((4-fluorophenyl)methyl)amino)carboxamide							
Compound 33	F	H	H	H	H	89	132
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((3,4-dimethoxyphenyl)methyl)amino)-carboxamide							
Compound 34	OMe	OMe	H	H	H	-	1010
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((3,4,5-trimethoxyphenyl)methyl)amino)-carboxamide							
Compound 35	OMe	OMe	H	OMe	H	-	2960

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N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((2-methylphenyl)methyl)amino)carboxamide							
Compound 36	H	H	Me	H	H	-	769
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(((4-methoxyphenyl)methyl)amino)carboxamide							
Compound 37	OMe	H	H	H	H	-	102

5

TABLE 9

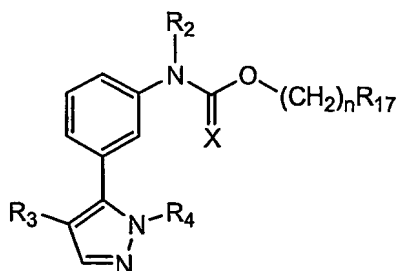


Compound Name							
Compound No.	R ₁₅	R ₁₄	R ₁₃	R ₁₆	R ₈	IP ₃ AP-3 IC ₅₀ nM	WT 5-HT _{2A} LSD IC ₅₀ nM
N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-(4-methoxyphenyl)ethyl)amino)carboxamide							
Compound 38	OMe	H	H	H	H	32	61

10

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[0198] A second series of compounds having 5-HT_{2A} receptor activity is represented by a class (II) of compounds of formula (B) wherein Y = O(CH₂)_nR₁₇.



(B2)

wherein:

5 Preferably R₂ is H.

Preferably R₃ is Br.

Preferably X is O.

Preferably R₄ is Me.

Preferably when n = 0, R₁₇ is 4-methoxyphenyl or tertiary butyl.

10 In some embodiments of the foregoing genus (B), class (II), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

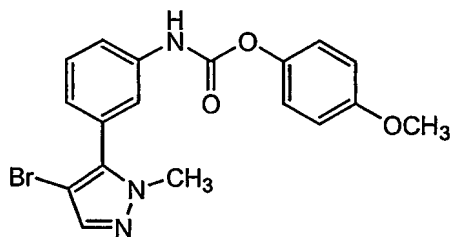
[0199] In some embodiments of the foregoing genus (B), class (II) compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0200] Certain preferred compounds are: .

15

Compound 1

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide

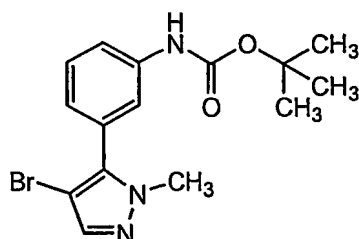


Compound 39

20

(tert-butoxy)-N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)carboxamide

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[0201] Compounds 1 and 39 demonstrated the following activity as illustrated in TABLE 10:

TABLE 10

Compound Number	Competitive Binding AP-1 ((³ H)mesulergine) IC ₅₀ Value (μM)	Competitive Binding WT 5-HT _{2A} ((³ H)LSD) IC ₅₀ Value (μM)	Inositol Phosphate Accumulation AP-3 IC ₅₀ Value (μM)
Compound 1	1.8	<0.001	0.0003
Compound 39	-	0.014	0.057

5

[0202] In addition to the assays discussed above, the specific activity of Compound 1 at the 5-HT_{2A} receptor was further confirmed by the following:

In Vitro Binding of 5-HT_{2A} Receptor

10 Animals:

[0203] Animals (Sprague-Dawley rats) were sacrificed and brains were rapidly dissected and frozen in isopentane maintained at -42° C. Horizontal sections were prepared on a cryostat and maintained at -20° C.

LSD Displacement Protocol:

15 [0204] Lysergic acid diethylamide (LSD) is a potent 5-HT_{2A} receptor and dopamine D2 receptor ligand. An indication of the selectivity of compounds for either or both of these receptors involves displacement of radiolabeled-bound LSD from pre-treated brain sections. For these studies, radiolabeled I¹²⁵-LSD (NEN Life Sciences, Boston, Mass., Catalogue number NEX-199) was utilized; spiperone (RBI, Natick, Mass. Catalogue number s-128) a 5-HT_{2A} receptor and dopamine D2 receptor antagonist, was also utilized. Buffer consisted of 50 nanomolar TRIS-HCl, pH 7.4.

20

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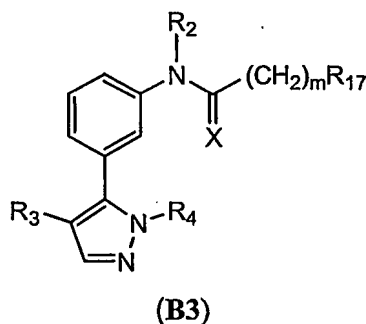
[0205] Brain sections were incubated in (a) Buffer plus 1 nanomolar I^{125} -LSD; (b) Buffer plus 1 nanomolar I^{125} -LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar I^{125} -LSD and 1 micromolar Compound 1 for 30 minutes at room temperature. Sections were then washed 2x 10 minutes at 4 ° C. in Buffer, followed by 20 seconds in distilled H_2O . Slides were then air-dried.

5 [0206] After drying, sections were apposed to x-ray film (Kodak Hyperfilm) and exposed for 4 days.

Analysis:

[0207] Figures 16A-C provide representative autoradiographic sections from this study. Figure 16A evidences darker bands (derived from I^{125} -LSD binding) primarily in both the fourth layer of the cerebral cortex (primarily 5-HT_{2A} receptors), and the caudate nucleus (primarily dopamine D2 receptors and some 5-HT_{2A} receptors). As can be seen from Figure 16B, spiperone, which is a 5-HT_{2A} and dopamine D2 antagonist, displaces the I^{125} -LSD from these receptors on both the cortex and the caudate. As can be further seen from Figure 16C, Compound 1 appears to selectively displace the I^{125} -LSD from the cortex (5-HT_{2A}) and not the caudate (dopamine D2).

15 [0208] A third series of compounds having 5-HT_{2A} receptor activity is represented by a class (III) of compounds of Formula (B3) wherein $Y=(CH_2)_mR_{17}$:



wherein

20 Preferably R_2 is H.
 Preferably R_3 is Br.
 Preferably X is O.
 Preferably R_4 is Me.

[0209] Preferably when $m=0$, R_{17} is preferably 4-trifluoromethoxyphenyl, or thiophene, or 4-chlorophenyl.

25 [0210] In some embodiments of the foregoing genus (B), class (III), compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

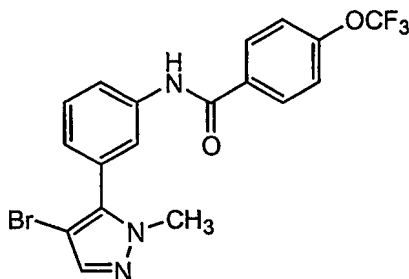
-60-

[0211] In some embodiments of the foregoing genus (B), class (III) compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0212] Certain preferred compounds are:

Compound 40 ($m = 0$, $R_2 = H$, $R_{17} = 4$ -trifluoromethoxyphenyl)

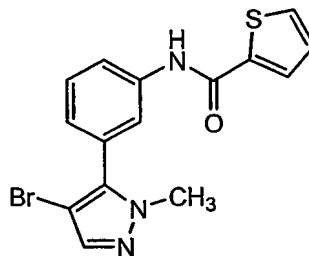
5 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-4-trifluoromethoxy-benzamide



10

Compound 2 ($m=0$, $R_2=H$, $R_{17}= \text{thiophene}$)

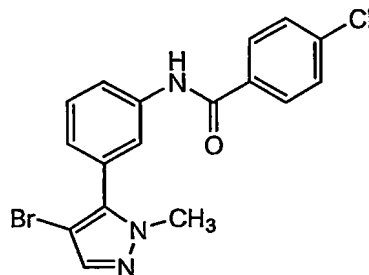
Thiophene-2-carboxylic acid [3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]amide



15

Compound 41 ($m=0$, $R_2=H$, $R_{17}= \text{chlorophenyl}$)

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-4-chloro-benzamide



20

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[0213] These three compounds demonstrated the following activities:

TABLE 11

Compound Number	Competitive Binding AP-1 ((³ H)mesulergine) IC ₅₀ Value (μ M)	Competitive Binding WT 5-HT _{2A} ((³ H)LSD) IC ₅₀ Value (μ M)	Inositol Phosphate Accumulation AP-3 IC ₅₀ Value (μ M)
Compound 40	6.1	.46	0.0213
Compound 2	2.8	.17	0.080
Compound 41	1.2	.21	0.0315

In Vivo Analysis of Compound 2

5 [0214] In addition to the in vitro assays shown in the above table, the in vivo response of animals to Compound 2 is demonstrated by the following.

[0215] A 5-HT_{2A} receptor antagonist or inverse agonist is expected to decrease amphetamine-stimulated locomotion without affecting baseline locomotion. See, for example, Soresnon, et al, 266(2) J. Pharmacol. Exp. Ther. 684 (1993). Based upon the foregoing information, Compound 2 is a
 10 potent inverse agonist at the human 5-HT_{2A} receptor. For the following study, the following parameters and protocol were utilized:

Animals, Vehicle

[0216] Adult male Sprague-Dawley rats were utilized for these studies. Animals were housed in groups of 2-3 in hanging plastic cages with food and water available at all times. Animals
 15 were weighed and handled for at least one day prior to surgery and throughout the studies. For these studies, Vehicle consisted of 90% ethanol (100%) and 10% water.

Amphetamine-Stimulated Locomotor Activity: Assessment and Apparatus

[0217] A San Diego Instruments Flex Field apparatus was used to quantify baseline and amphetamine-stimulated locomotor activity. This apparatus consists of four 16" x 16" clear plastic
 20 open fields. Photocell arrays (16 in each dimension) interfaced with a personal computer to automatically quantify activity. Several measures of activity can be assessed with the apparatus, including total photocell beam breaks. Animals (vehicle control and Compound treated) were injected

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s.c. 30 minutes prior to initiation of analysis. Following this 30 minute period, animals were placed individually into an open field and baseline activity was assessed for 30 minutes (habituation phase). Following baseline, animals were removed, injected with d-amphetamine sulfate (1.0 mg/kg) and immediately returned to the open field for 150 minutes, in order to follow the time course (10 minute intervals) of amphetamine-stimulated locomotor activity.

Dosing

TABLE 12

Vehicle Control	Compound 2	Dose (mg/kg)
6 animals	6 animals	0.1
	6 animals	1.0
	6 animals	5.0
	6 animals	10.0

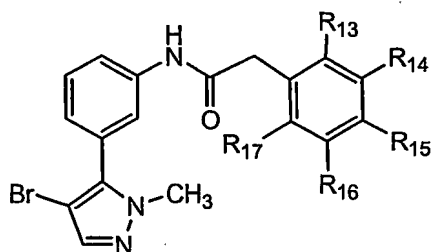
Analysis

10 [0218] Results, based upon the number of recorded photobeam breaks (mean. \pm sem), are presented in Figures 17A-C. As supported by Figures 17A, B and C, a general "inverted U" shaped pattern was observed (see, generally, Sahgal, A. "Practical behavioural neuroscience: problems, pitfalls and suggestions" pp 1-8, 5 in Behavioral Neuroscience: A Practical Approach, Volume 1 A. Sahgal (Ed.) 1993, IRL Press, New York). As Figure 17 also indicates, with exception of the highest dose (10 mg/kg), in vivo, the tested doses of Compound 2 evidenced a decrease in the amphetamine-stimulated locomotion, consistent with a 5-HT_{2A} receptor antagonist or inverse agonist.

[0219] Additional series of compounds of Formula (B) wherein Y=(CH₂)_mR₁₇ are set forth below in TABLE 13.

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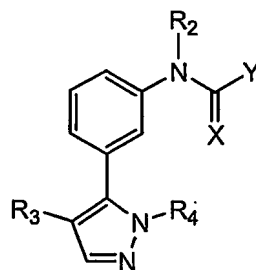
TABLE 13



Name	Compound No.	R ₁₅	R ₁₄	R ₁₃	R ₁₆	IP ₃ AP-3 IC ₅₀ nM	WT 5-HT _{2A} LSD IC ₅₀ nM
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy)-phenyl)acetamide	Compound 42	OCF ₃	H	H	H	-	106
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(3-Fluorophenyl)acetamide	Compound 43	H	F	H	H	153	318
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(3-Methoxyphenyl)acetamide	Compound 44	H	OMe	H	H	108	625
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(2-Fluorophenyl)acetamide	Compound 45	H	H	F	H	129	662
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(4-Nitrophenyl)acetamide	Compound 46	NO ₂	H	H	H	61	108
N-(3-(4-bromo-2-Methylpyrazol-3-yl)phenyl)-2-(2-Methoxyphenyl)acetamide	Compound 47	H	H	OMe	H	165	2300

[0220] Based upon the discovery of the specific inverse agonist activity of the above identified compounds at the 5-HT_{2A} receptor, a novel class of compounds has been identified which exhibits said activity. Accordingly, in the second aspect of the invention, there is provided a novel compound of formula (C):

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(C)

wherein:

R^2 is H or lower alkyl(C_{1-4});

R_3 is Me, or Et, or halogen;

5 X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH_2)_m R_{17}$, or $O(CH_2)_n R_{17}$;

R_4 is lower alkyl (C_{1-6});

$m=0-4$;

$n=0-4$;

10 R_{15} is H or lower alkyl(C_{1-4});

R_{16} is a C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or $(CH_2)_k$ aryl group ($k=1-4$), preferably $k=1$, and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{20}$, SO_3R_{20} , $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, aryl and aryloxy may be further substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{20}$, SO_3R_{20} , $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

20 R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{23}$, SO_3R_{23} , $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{23}$, SO_3R_{23} , $SO_2NR_{21}R_{22}$,

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COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

or R₁₈ and R₁₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₇, SO₂NR₂₁R₂₂, SO₃R₂₃, NHCOCH₃, COEt, COMe, or halogen;

R₁₇ is C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

R₂₀ and R₂₃ may be independently selected from H or C₁₋₆ alkyl;

R²¹ and R²² are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₂₀, SO₃R₂₀, COEt, NHCOCH₃, or aryl. An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle;

C₁₋₆ alkyl moieties can be straight chain or branched;

optionally substituted C₁₋₆ alkyl moieties can be straight chain or branched;

C₂₋₆ alkenyl moieties can be straight chain or branched; and

optionally substituted C₂₋₆ alkenyl moieties can be straight chain or branched;

Examples of suitable C₁₋₆ alkyl groups include but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, and t-butyl.

[0221] Halogens are typically F, Cl, Br, and I.

[0222] Examples of 5 or 6 membered ring moieties include, but are not restricted to, phenyl, furanyl, thienyl, imidazolyl, pyridyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrazolyl, tetrazolyl,

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thiazolyl and isothiazolyl. Examples of polycycle moieties include, but are not restricted to, naphthyl, benzothiazolyl, benzofuranyl, benzimidazolyl, quinolyl, isoquinolyl, indolyl, quinoxaliny, quinazolinyl and benzothienyl.

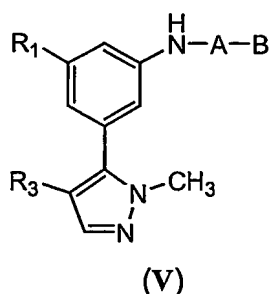
[0223] In some embodiments of the foregoing genus (C), compounds of Example 13,
5 Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0224] In some embodiments of the foregoing genus (C), compounds of Example, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0225] Some embodiments of the invention are compounds of Formula (V) and have one of the structures below.

10

TABLE 14



Cmpd	R ₁	R ₃	A	B
Compound Name				
48	H	Cl	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
49	Cl	Cl	C(=O)	-NH-(4-chlorophenyl)
1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
50	H	Cl	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea				
51	H	Cl	C(=O)	-NH-CH(CH ₃)-phenyl
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea				
52	H	Cl	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea				

15

53	H	Cl	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea				
54	H	Cl	C(=O)	-NH-(4-ethoxycarbonyl)phenyl
4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester				
55	H	Cl	C(=O)	-NH-(4-methylthio)phenyl
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea				
56	H	Cl	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
57	H	I	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
58	H	Br	C(=O)	-O-ethyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester				
59	H	Br	C(=O)	-O-(4-nitro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester				
60	H	Br	C(=O)	-O-CH ₂ -fluorene-9-yl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9H-fluorene-9-ylmethyl ester				
61	H	Br	C(=O)	-O-CH ₂ CH=CH ₂
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester				
62	H	Br	C(=O)	-O-(4-methyl)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester				
63	H	Br	C(=O)	-O-n-butyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester				
64	H	Br	C(=O)	-O-(2-isopropyl-5-methyl)cyclohex-1-yl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester				
65	H	Br	C(=O)	-O-benzyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester				
66	H	Br	C(=O)	-O-(3-trifluoromethyl)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester				

67	H	Br	C(=O)	-O-(4-bromo)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester				
68	H	Br	C(=O)	-O-(4-fluoro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester				
69	H	Br	C(=O)	-O-(2-methoxy)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester				
70	H	Br	C(=O)	-O-(2-chloro)phenyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester				
71	H	Br	C(=O)	-O-C(CH ₃)=CH ₂
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester				
72	H	Br	C(=O)	-O-1-(N-pyridinyl)ethyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl ester				
73	H	Br	C(=O)	-O-isopropyl
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester				
74	H	-C(=O)OCH ₃	C(=O)	-NH-(4-chlorophenyl)
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid methyl ester				
75	H	-CH ₂ CH ₂ OH	C(=O)	-NH-(4-fluorophenyl)
1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
76	H	-CH ₂ CH ₂ N(Me) ₂	C(=O)	-NH-(4-fluorophenyl)
1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-phenyl)-urea				
77	H	-CH=CH ₂	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea				
78	H	CH ₂ CH ₃	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
79	H	-CH=CH ₂	C(=O)	-NH-(4-fluorophenyl)
1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea				
80	H	Phenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea				
81	H	4-methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
82	H	3-methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				

83	H	4-fluorophenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea				
84	H	4-trifluoro methoxyphenyl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-phenyl}-urea				
85	H	Thiophen-2-yl	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea				
86	H	-C(=O)-OH	C(=O)	-NH-(4-chlorophenyl)
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid				
87	H	Cyclopropyl	C(=O)	-NH-(3- trifluoromethylphenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea				
88	H	Cyclopropyl	C(=O)	-NH-(3-chlorophenyl)
1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
89	H	Cyclopropyl	C(=O)	-NH-(2-methoxyphenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea				
90	H	-CCH	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
91	H	-CH=CH-CCH	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
92	H	-CH=CH-CCH	C(=O)	-NH-(4-methylphenyl)
1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea				
93	H	CN	C(=O)	-NH-(4-chlorophenyl)
1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea				
94	H	CN	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
95	H	Cyclopropyl	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea				
96	F	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea				
97	F	Br	SO ₂	4-fluorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-benzenesulfonamide				

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98	F	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea				
99	F	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea				
100	F	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea				
101	F	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea				
102	F	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea				
103	F	Br	SO ₂	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-benzenesulfonamide				
104	F	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-urea				
105	-N(Me) ₂	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-phenyl)-urea				
106	Pyrrolidin-1-yl	Br	C(=O)	-NH-CH(CH ₃)-phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea				
107	Morpholin-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea				
108	Pyrrolidin-1-yl	Br	C(=O)	Phenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide				
109	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-phenyl)-urea				
110	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-dimethylamino-phenyl)-urea				
111	Morpholin-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-phenyl)-urea				

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112	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-bromophenyl)-urea				
113	-N(Me) ₂	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-phenyl)-urea				
114	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2-trifluoromethoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-trifluoromethoxy-phenyl)-urea				
115	Pyrrolidin-1-yl	Br	C(=S)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-thiourea				
116	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea				
117	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea				
118	Pyrrolidin-1-yl	Br	SO ₂	4-fluorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluoro-benzenesulfonamide				
119	-N(Me) ₂	Br	SO ₂	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chloro-benzenesulfonamide				
120	Morpholin-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluoro-phenyl)-urea				
121	Morpholin-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chloro-phenyl)-urea				
122	Pyrrolidin-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea				

123	-N(Me) ₂	Br	C(=O)	-NH-(4-dimethylamino-phenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea				
124	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea				
125	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea				
126	Morpholin-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
127	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea				
128	Morpholin-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-urea				
129	-N(Me) ₂	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-urea				
130	-N(Me) ₂	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-phenyl)-urea				
131	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-urea				
132	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
133	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea				

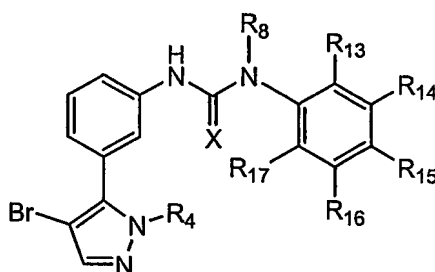
134	Morpholin-1-yl	Br	C(=O)	-NH-(4-trifluoromethylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea				
135	Pyrrolidin-1-yl	Br	C(=O)	-NH-(3-amino-4-fluorophenyl)
1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-urea				
136	-N(Me) ₂	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-phenyl)-urea				
137	Pyrrolidin-1-yl	Br	C(=O)	-NH-(3-nitro-4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-phenyl)-urea				
138	-N(Me) ₂	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-urea				
139	Pyrrolidin-1-yl	Br	C(=O)	-NH-CH(CH ₃)-phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-urea				
140	Pyrrolidin-1-yl	Br	C(=O)	-NH-(2-phenyl)cycloprop-1-yl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea				
141	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-urea				
142	Morpholin-1-yl	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-phenyl)-urea				
143	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-urea				
144	-N(Me) ₂	Br	SO ₂	4-fluorophenyl)
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-benzenesulfonamide				
145	Pyrrolidin-1-yl	Br	SO ₂	Phenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzenesulfonamide				
146	Morpholin-1-yl	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-phenyl)-urea				

147	4-methylpiperazine-1-yl	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea				
148	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-isopropylphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-phenyl)-urea				
149	-OMe	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea				
150	-OH	Br	C(=O)	-NH-(3,5-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-urea				
151	-OH	Br	C(=O)	-NH-(4-fluorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea				
152	-OMe	Br	SO ₂	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-benzenesulfonamide				
153	-OMe	Br	C(=O)	-NH-(4-dimethylaminophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-phenyl)-urea				
154	-OMe	Br	C(=O)	-NH-(4-bromophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea				
155	-OH	Br	SO ₂	4-chlorophenyl
N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-benzenesulfonamide				
156	-OMe	Br	C(=O)	-NH-(3,5-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-urea				
157	-OH	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea				
158	-OMe	Br	C(=O)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea				
159	-OMe	Br	C(=O)	-NH-(2,4-dichlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-urea				
160	Pyrrolidin-1-yl	Br	C(=O)	-NH-(4-trifluoromethyl)phenyl
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-trifluoromethyl-phenyl)-urea				

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161	-OH	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-urea				
162	-OMe	Br	C(=O)	-NH-(4-methoxyphenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-urea				
163	-OH	Br	C(=O)	-NH-(4-cyanophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea				
164	H	Br	C(=S)	-NH-(4-chlorophenyl)
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea				

[0226] Also provided in accordance with the present invention are compounds useful as inverse agonists for 5-HT_{2A} receptors having the structure:



5 wherein:

X is O or S;

R₄ is H or CH₃;

R₈ and R₃₀ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₈ alkenyl;

10 R₁₅ is H, F, Cl, Br, I, R₂₀, CF₃, CCl₃, NR₁₈R₁₉, NR₃₀COR₂₀, NR₃₀SO₂R₂₀, OR₂₀, OCF₃, OCOR₂₀, OSO₂R₂₀, SR₂₀, SCF₃, SCOR₂₀, SO₃R₂₀, SO₂NR⁸R⁹, NO₂, CN, COOR₂₀, COSR₂₀, or CONR₁₈R₁₉,

with the proviso that when a position adjacent to R₁₅ is substituted, then R₁₅ and said adjacent position can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or

15 OCH₂CH₂O to form a bi-cyclic structure;

R₂₀ is H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, C₂₋₈ alkenyl, aryl or alkylaryl;

20 R₁₈ and R₁₉ are each independently selected from: H, C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂,

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NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂,

10 with the proviso that when either of R₁₈ or R₁₉ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently selected from the following: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

25 with the proviso that when any two adjacent positions of R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are substituted, said two adjacent positions can together be further selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

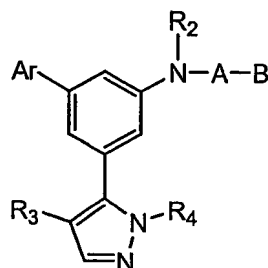
with the proviso that at least two of R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ must be H.

[0227] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0228] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

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[0229] In some embodiments, compounds possessing 5-HT_{2A} receptor activity that are useful as inverse agonists at such receptors are designated by the general Formula (XV):



(XV)

5 wherein:

- i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR₇, OH, NR₈R₉, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl -C(p)₃, or -O-C(p)₃ where p is halogen;

10 R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl; or

15 R₈ and R₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

20 R₇ is H or C₁₋₆ alkyl;

R₁₀ is H or C₁₋₆ alkyl;

- ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

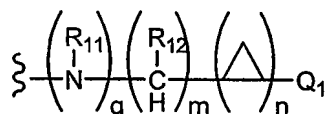
25 iii) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can

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alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

- iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;
 v) A is $C(=O)$, $C(=S)$ or SO_2 ;
 5 vi) B is L_1 or L_2 ;

L_1 is:



q is 0 or 1;

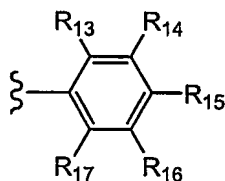
m is 0 or 1;

10

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



15

wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

25

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_7 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl,

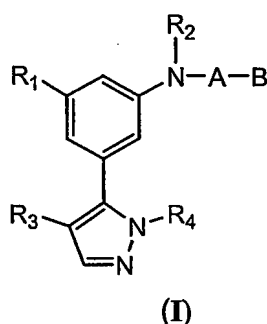
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alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

5 Methods

[0230] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



10 wherein:

i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

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R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3 , OCF_3 , OEt, CCl_3 , Me, NO_2 , OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10} , COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10} , NR_8R_9 , halogen,

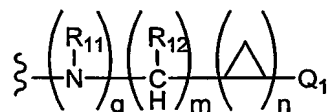
$-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is $C(=O)$, $C(=S)$ or SO_2 ;

vi) B is L_1 or L_2 ;

L_1 is:



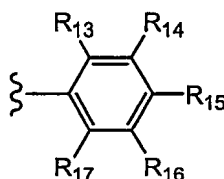
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6}

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5 alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

10 L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, 15 alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

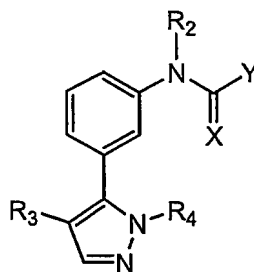
[0231] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic 20 ring or a polycycle.

[0232] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0233] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

25 [0234] Also provided by the present invention are methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:

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(A)

wherein:

R_2 is H or lower alkyl(C_{1-4});

R_3 is lower alkyl (C_{1-6}), or halogen;

5 R_4 is lower alkyl (C_{1-6});

X is either Oxygen or Sulfur;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

$m=0-4$

$n=0-4$

10 R_{15} is H or lower alkyl(C_{1-4});

R_{16} and R_{17} are independently C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{18}R_{19}$, $NR_{18}R_{19}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{20}$, SO_3R_{20} , $SO_2NR_{18}R_{19}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

15 R_{18} and R_{19} are independently a H or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_{21}R_{22}$, $NR_{21}R_{22}$, $NHCOCH_3$, OCF_3 , SMe, $COOR_{23}$, SO_3R_{23} , $SO_2NR_{21}R_{22}$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl;

20 or R_{18} and R_{19} may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, OCF_3 , SMe, $COOR_{23}$, $SO_2NR_{21}R_{22}$, SO_3R_{23} , $NHCOCH_3$, COEt, COMe, or halogen;

25

R_{20} and R_{23} are each independently selected from H or C_{1-6} alkyl;

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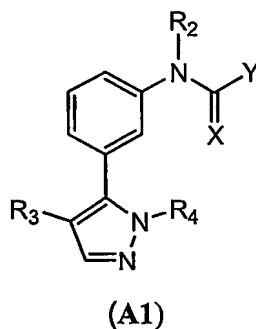
R_{21} and R_{22} are each independently are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3 , OCF_3 , OEt, CCl_3 , Me, NO_2 , OH, OMe, SMe, COMe, CN, $COOR_{20}$, SO_3R_{20} , COEt, $NHCOCH_3$, or aryl;

an aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0235] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0236] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0237] The present invention further provides methods for modulating the activity of a human $5-HT_{2A}$ serotonin receptor by contacting the receptor with a compound of formula:



wherein:

R_3 is F, Cl, Br, I, C_{1-6} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-6} alkenyl;

X is O or S;

Y is $NR_{15}R_{16}$, or $(CH_2)_mR_{17}$, or $O(CH_2)_nR_{17}$;

m is an integer between 0 and 4, inclusive;

n is an integer between 0 and 4, inclusive;

R_4 is H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

R_2 and R_{15} are each independently selected from H, C_{1-8} straight chain or branched alkyl, C_{3-8} cycloalkyl, C_{4-9} alkylcycloalkyl, or C_{2-8} alkenyl;

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R₁₆ and R₁₇ is each independently selected from: C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: H, F, Cl, Br, I, R₂₀, CF₃, CF₂R₇, CF₂CF₂, CCl₃, CCl₂R₇, CCl₂CCl₂R₇, NR₁₈R₁₉, NR₁₈COR₂₀, NR₁₈SO₂R₂₀, OR₂₀, OCF₃, OCF₂R₂₀, OCF₂CF₂R₂₀, OCOR₂₀, OSO₂R₂₀, OPO(OR₂₀)₂, SR₂₀, SCF₃, SCF₂R₂₀, SCF₂CF₂R₂₀, SCOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, PO(OR₂₀)₃, PO(OR₂₀)₂R₂₀, NO₂, CN, CNR₂₀(NR₁₈R₁₉), CNR₁₈(SR₂₀), COOR₂₀, COSR₂₀, CONR₁₈R₁₉,

with the proviso that when R₁₆ or R₁₇ contains an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₂₀ is H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, C₂₋₈ alkenyl, aryl or alkylaryl;

R₁₈ and R₁₉ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃, NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

with the proviso that when either or both of R₁₈ or R₁₉ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

or

R₁₈ or R₁₉ may together form part of a 5, 6 or 7 membered cyclic structure, with said structure being saturated or unsaturated, and further with said structure containing up to four heteroatoms

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selected from O, N or S, and further wherein each moiety within said cyclic structure being optionally substituted by up to four substituents in any position independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NH₂SO₂CH₃, NH₂SO₂C₂H₅, NH₂SO₂C₃H₇, NH₂SO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉, OC₅H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

with the proviso that wherein when R₁₈ or R₁₉ form an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure.

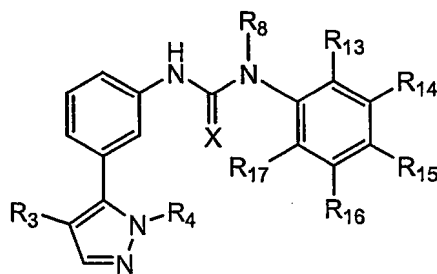
[0238] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0239] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0240] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0241] Also provided by the present invention are methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:

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(A2)

wherein:

X is O or S;

R₄ is H or CH₃;

- 5 R₈ and R₂₀ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₃₋₈ cycloalkyl, C₄₋₉ alkylcycloalkyl, or C₂₋₈ alkenyl;

- R₁₅ is H, F, Cl, Br, I, R₂₀, CF₃, CF₂R₂₀, CF₂CF₂, CCl₃, CCl₂R₂₀, CCl₂CCl₂R₂₀, NR₁₈R₁₉, NR₁₉COR₂₀, NR₁₉SO₂R₂₀, OR₂₀, OCF₃, OCF₂R₂₀, OCF₂CF₂R₂₀, OCOR₂₀, OSO₂R₂₀, OPO(OR₂₀)₂, SR₂₀, SCF₃, SCF₂R₂₀, SCF₂CF₂R₂₀, SCOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, PO(OR₂₀)₃, PO(OR₂₀)₂R₂₀, NO₂,
 10 CN, CNR₂₀(NR₁₈R₁₉), CNR₁₉(SR₂₀), COOR₂₀, COSR₂₀, CONR₁₈R₁₉,

with the proviso that when a position adjacent to R₁₅ is substituted, then R₁₅ and said adjacent position can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

- R₁₈ and R₁₉ are each independently selected from H, C₁₋₈ straight chain or branched alkyl, C₂₋₈
 15 alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl, or CH₂aryl, wherein each moiety within said C₁₋₈ straight chain or branched alkyl, C₂₋₈ alkenyl or cycloalkyl, or alkylcycloalkyl, or aryl or CH₂aryl may be optionally substituted by up to four substituents in any position, whereby each substituent is independently selected from: F, Cl, Br, I, CF₃, CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂, NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHCO₂CH₃, NHCO₂C₂H₅, NHCO₂C₃H₇, NHCO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅, OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₁₁, SC₆H₁₃, SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH, SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅,
 20 SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂, SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃, COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂, CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

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with the proviso that when either or both of R₁₈ or R₁₉ contain an aryl ring substituted at at least two adjacent positions on said aryl ring, then said two adjacent positions can together be selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure;

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ each independently selected from the following: F, Cl, Br, I, CF₃,
 5 CCl₃, CH₃, C₂H₅, C₃H₇, C₄H₉, NH₂, NHCH₃, N(CH₃)₂, NHC₂H₅, N(C₂H₅)₂, NHC₃H₇, N(C₃H₇)₂,
 NHC₄H₉, N(C₄H₉)₂, NHCOH, NHCOCH₃, NHCOC₂H₅, NHCOC₃H₇, NHCOC₄H₉, NHSO₂CH₃,
 NHSO₂C₂H₅, NHSO₂C₃H₇, NHSO₂C₄H₉, OH, OCH₃, OC₂H₅, OC₃H₇, OC₄H₉, OC₅H₉,
 OC₃H₁₁, OC₆H₁₁, OC₆H₁₃, OCF₃, OCOCH₃, OCOC₂H₅, OCOC₃H₇, OCOC₄H₉, OSO₂CH₃, OSO₂C₂H₅,
 OSO₂C₃H₇, OSO₂C₄H₉, SH, SCH₃, SC₂H₅, SC₃H₇, SC₄H₉, SC₅H₉, SC₅H₁₁, SC₆H₁₁, SC₆H₁₃,
 10 SCF₃, SCOCH₃, SCOC₂H₅, SCOC₃H₇, SCOC₄H₉, SO₃CH₃, SO₃C₂H₅, SO₃C₃H₇, SO₃C₄H₉, SO₂NH,
 SO₂NH₂, SO₂NHCH₃, SO₂N(CH₃)₂, SO₂NHC₂H₅, SO₂N(C₂H₅)₂, SO₂NHC₃H₇, SO₂N(C₃H₇)₂,
 SO₂NHC₄H₉, SO₂N(C₄H₉)₂, NO₂, CN, COOCH₃, COOC₂H₅, COOC₃H₇, COOC₄H₉, COSCH₃,
 COSC₂H₅, COSC₃H₇, COSC₄H₉, CONH₂, CONHCH₃, CON(CH₃)₂, CONHC₂H₅, CON(C₂H₅)₂,
 CONHC₃H₇, CON(C₃H₇)₂, CONHC₄H₉, CON(C₄H₉)₂, and

15 with the proviso that when any two adjacent positions of R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are substituted, said two adjacent positions can together be further selected from SCH₂S, SCH₂CH₂S, OCH₂O, or OCH₂CH₂O to form a bi-cyclic structure; and

with the proviso that at least one of R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ must be H.

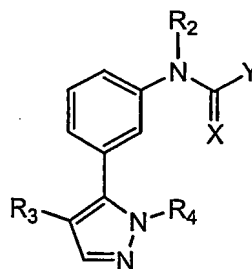
[0242] An aryl moiety can be a 5 or 6 membered aromatic heterocyclic ring (containing up to
 20 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0243] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

[0244] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0245] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:

-88-



(B)

wherein:

R₂ is H or lower alkyl (C₁₋₄);

R₃ is Me, or Et, or halogen;

5 X is either Oxygen or Sulfur;

Y is NR₁₅R₁₆, or (CH₂)_mR₁₇, or O(CH₂)_nR₁₇;

R₄ is lower alkyl (C₁₋₆);

m=0-4

n=0-4

10 R₁₅ is H or lower alkyl (C₁₋₄);

R₁₆ and R₁₇ are independently C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₁₈R₁₉, NR₁₈R₁₉, NHCOCH₃, OCF₃, SMe, COOR₂₀, SO₃R₂₀, SO₂NR₁₈R₁₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, aryl and aryloxy wherein each of the C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, aryl and aryloxy groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl;

20 R₁₈ and R₁₉ are independently a H or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₂₁R₂₂, NR₂₁R₂₂, NHCOCH₃, OCF₃, SMe, COOR₂₃, SO₃R₂₃, SO₂NR₂₁R₂₂, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl

25

or R₁₈ and R₁₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up

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to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₇, SO₂NR₂₄R₂₅, SO₃R₂₆, NHCOCH₃, COEt, COMe, or halogen;

R₂₀ and R₂₃ are each independently selected from H or C₁₋₆ alkyl;

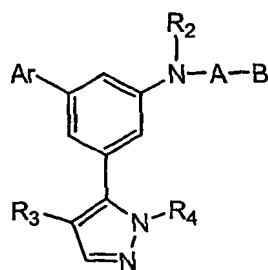
- 5 R₂₁ and R₂₂ are each independently are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₂₀, SO₃R₂₀, COEt, NHCOCH₃, or aryl.

- 10 [0246] An aryl moiety can be a 5 or 6 membered aromatic hetero-cyclic ring (containing up to 4 hetero atoms independently selected from N, O, or S) or a 6 membered aromatic non-heterocyclic ring or a polycycle.

[0247] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

- 15 [0248] In some embodiments of the foregoing genus, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0249] The present invention further provides methods for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of formula:



(XV)

- 20 wherein:

- ii) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR₇, OH, NR₈R₉, carboxy, CN, alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl -C(p)₃, or -O-C(p)₃ where p is halogen;

- 25 R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃,

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OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl; or

R₈ and R₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₇ is H or C₁₋₆ alkyl;

R₁₀ is H or C₁₋₆ alkyl;

ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

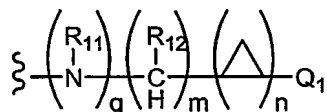
iv) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO₂;

vi) B is L₁ or L₂;

L₁ is:



q is 0 or 1;

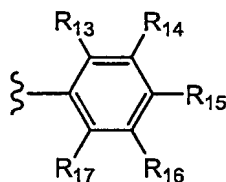
m is 0 or 1;

n is 0 or 1;

R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

Q₁ is:

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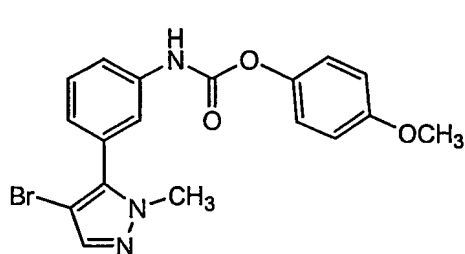
wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

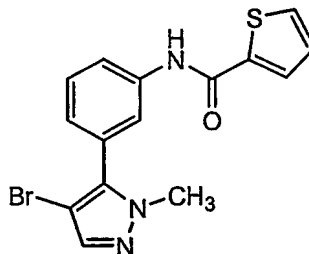
L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_7 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

[0250] In some embodiments of the foregoing methods, the compounds are selected from compounds and combinations and subcombinations of compounds selected from the group consisting of:

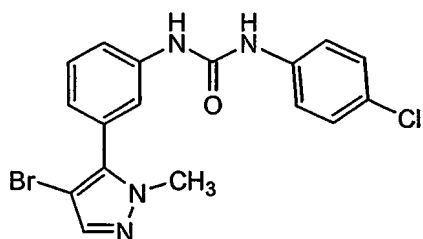


Compound 1

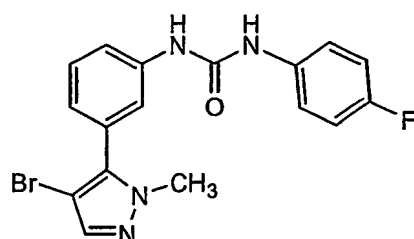


Compound 2

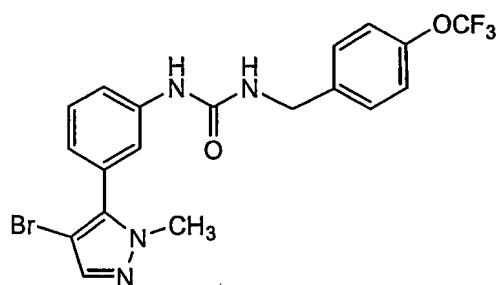
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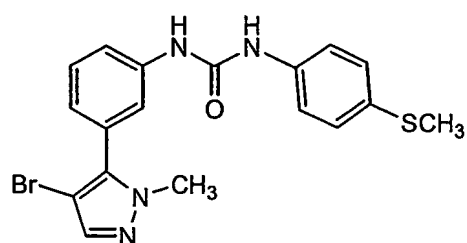
Compound 8



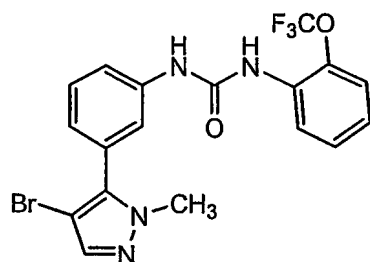
Compound 9



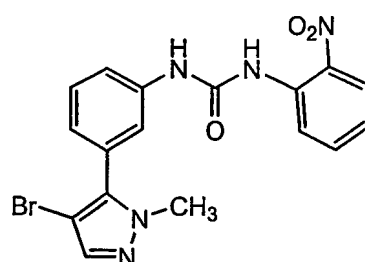
Compound 10



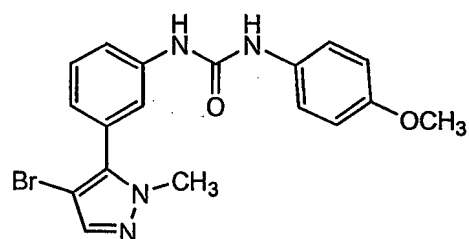
Compound 11



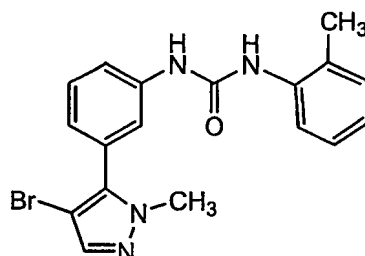
Compound 12



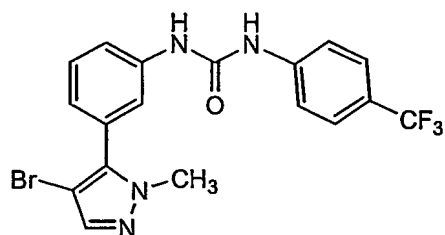
Compound 13



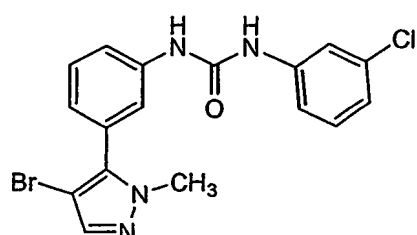
Compound 14



Compound 15



Compound 16

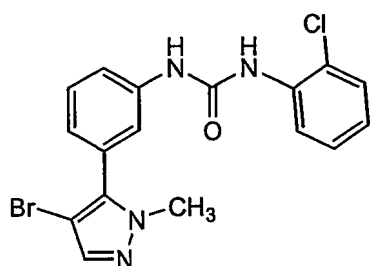


Compound 17

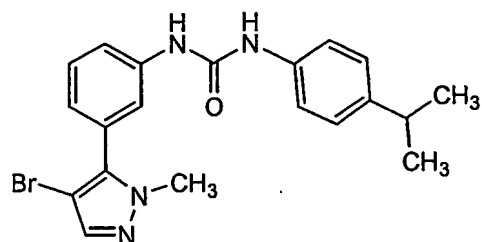
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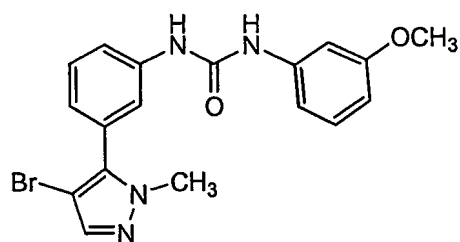
-93-



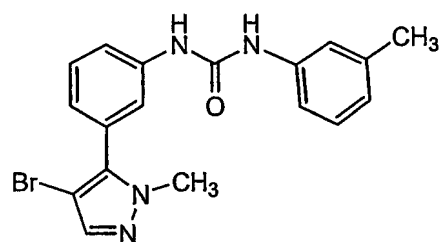
Compound 18



Compound 19

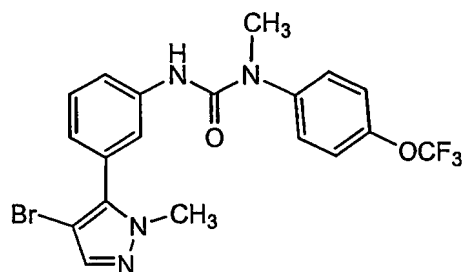


Compound 20

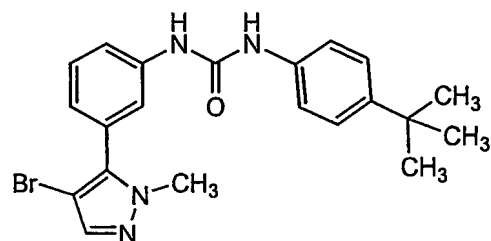


Compound 21

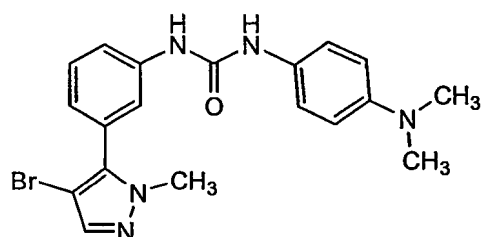
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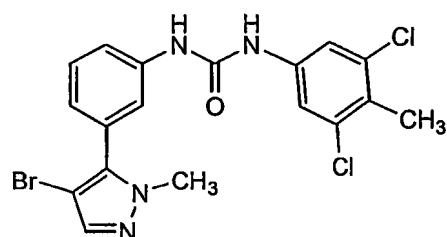
Compound 22



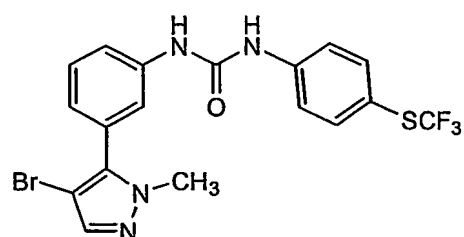
Compound 23



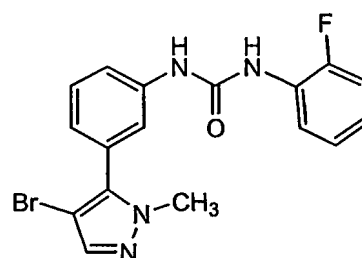
Compound 24



Compound 25



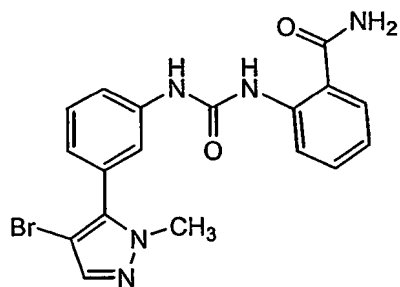
Compound 26



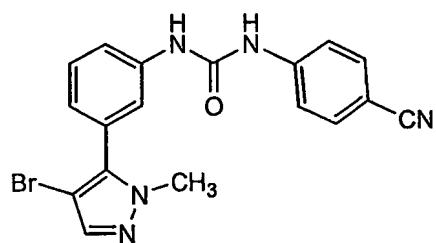
Compound 27

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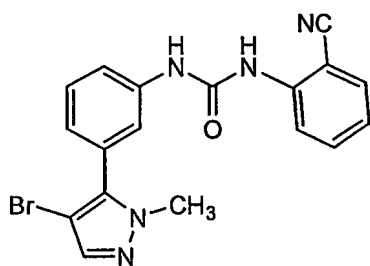
-94-



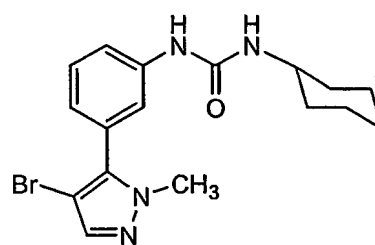
Compound 28



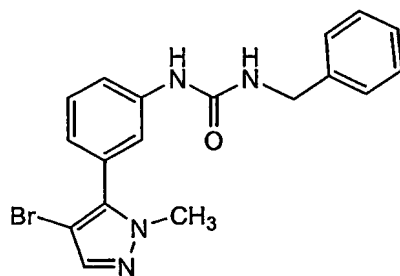
Compound 29



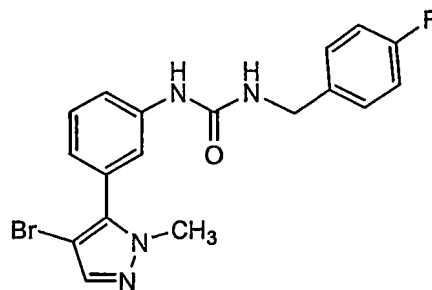
Compound 30



Compound 31

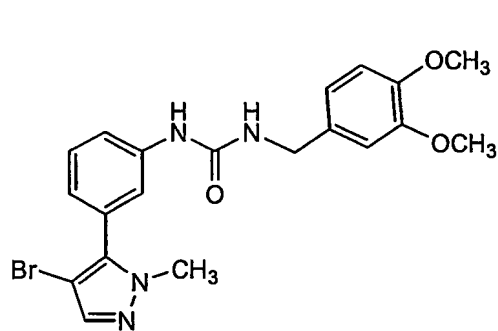


Compound 32

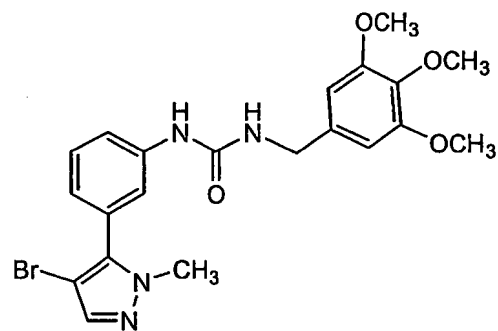


Compound 33

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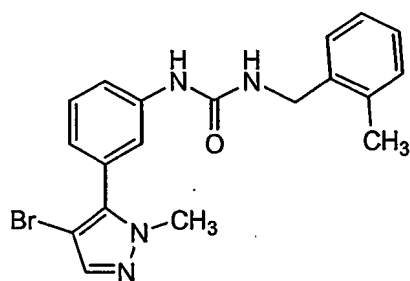


Compound 34

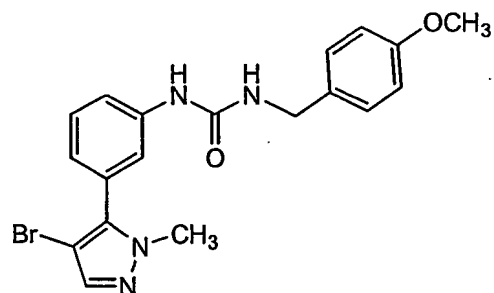


Compound 35

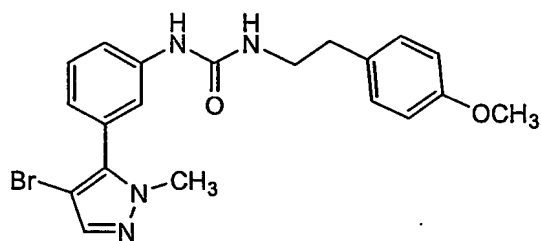
-95-



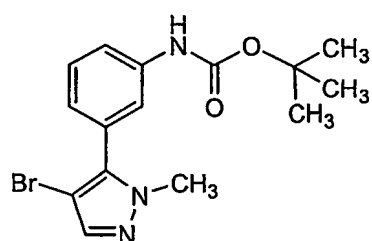
Compound 36



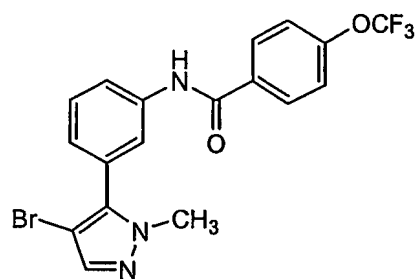
Compound 37



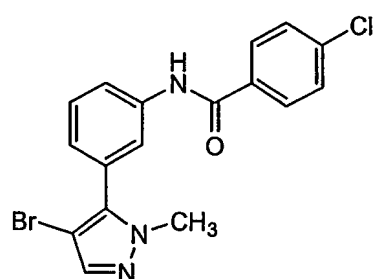
Compound 38



Compound 39

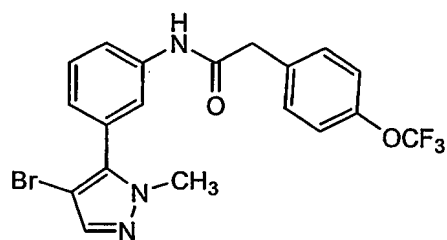


Compound 40

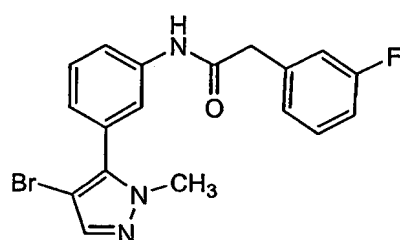


Compound 41

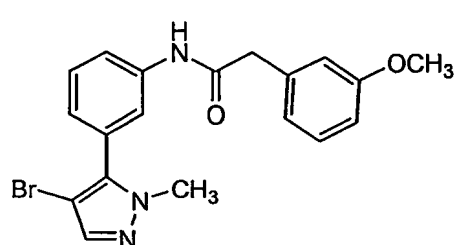
5



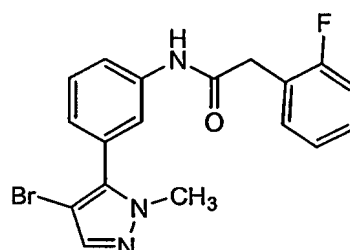
Compound 42



Compound 43

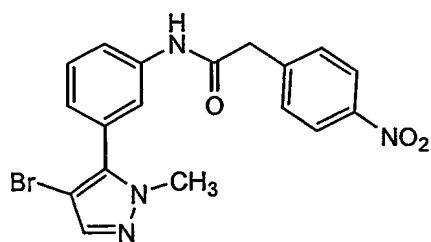


Compound 44

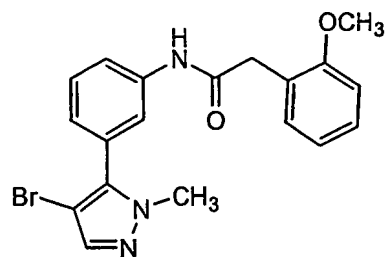


Compound 45

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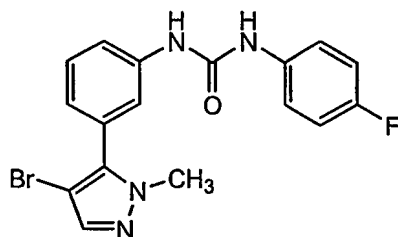
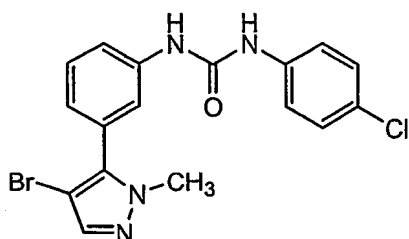
Compound 46



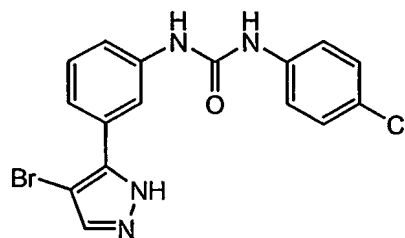
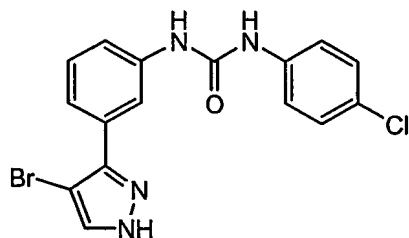
Compound 47

[0251] In some embodiments, the present invention provides the foregoing compounds, and combinations and subcombinations thereof.

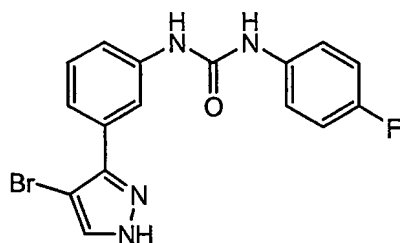
- 5 [0252] In some preferred embodiments, the present invention provides compounds useful as inverse agonists for 5-HT_{2A} receptors structurally represented as follows:



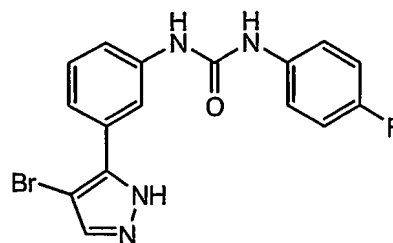
10



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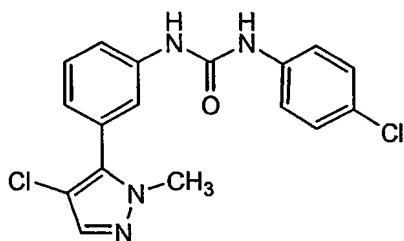


and

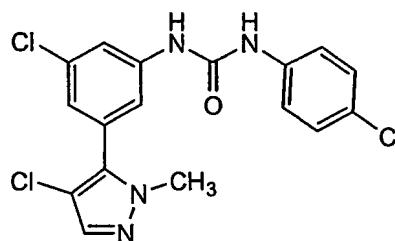


[0253] Also provided by the present invention are compositions comprising each of the compounds of the invention.

- 5 [0254] Other preferred compounds provided by the present invention and useful in the methods disclosed herein, include, but are not limited to:

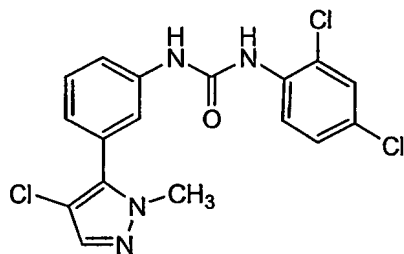


Compound 48

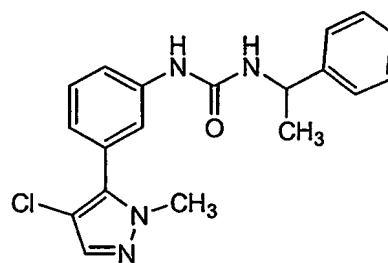


Compound 49

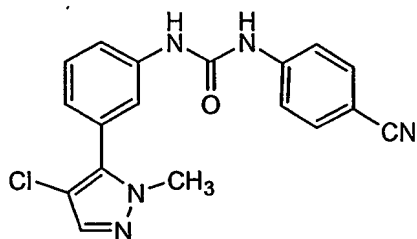
10



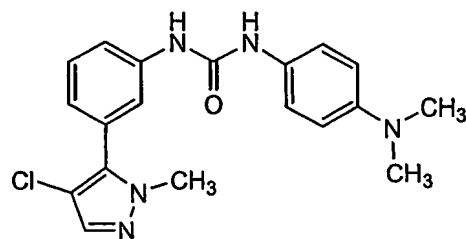
Compound 50



Compound 51



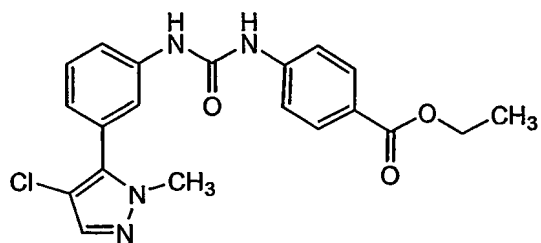
Compound 52



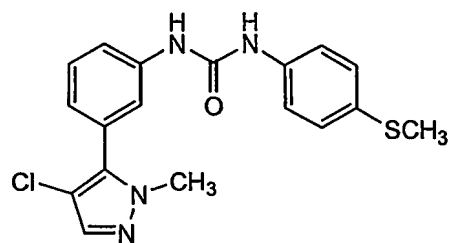
Compound 53

15

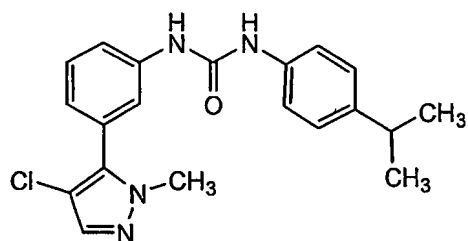
-98-



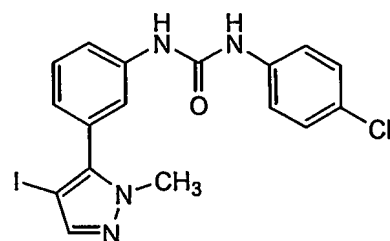
Compound 54



Compound 55

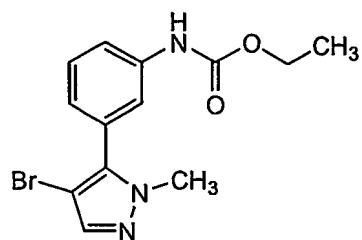


Compound 56

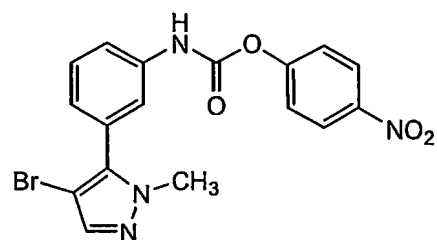


Compound 57

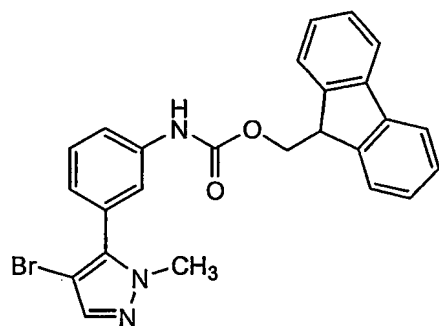
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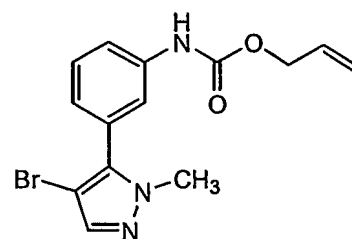
Compound 58



Compound 59



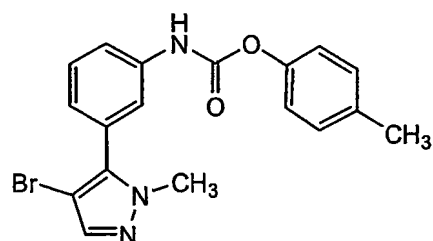
Compound 60



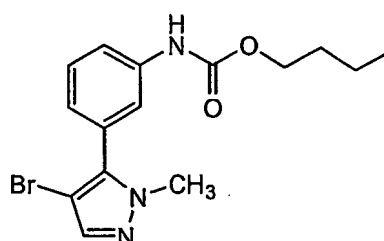
Compound 61

10

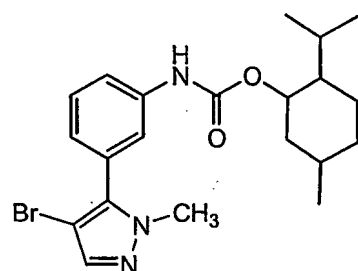
-99-



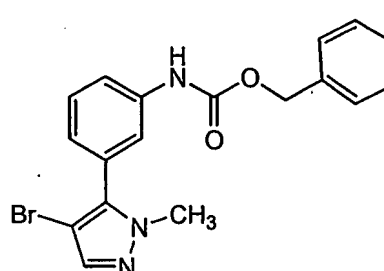
Compound 62



Compound 63

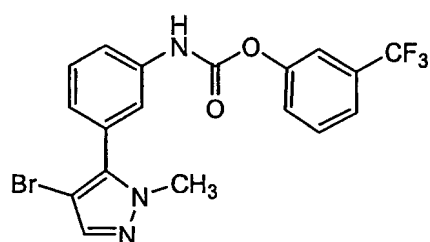


Compound 64

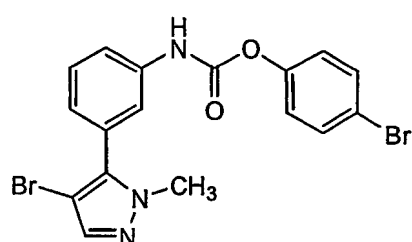


Compound 65

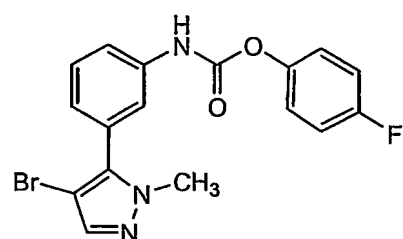
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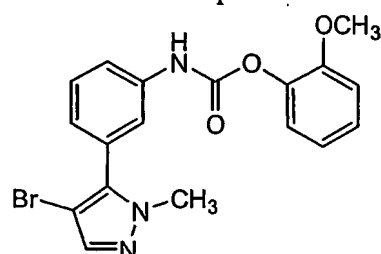
Compound 66



Compound 67

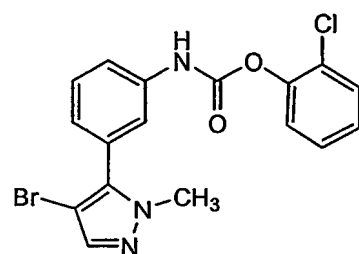


Compound 68

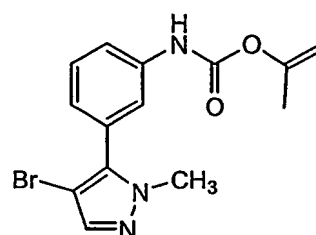


Compound 69

10

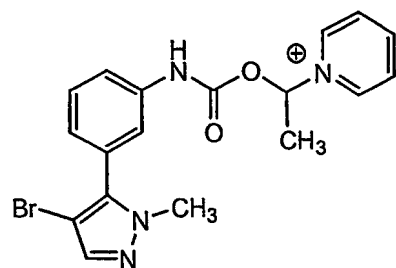


Compound 70

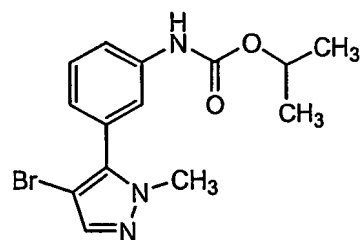


Compound 71

-100-

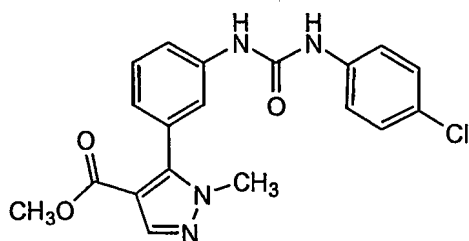


Compound 72

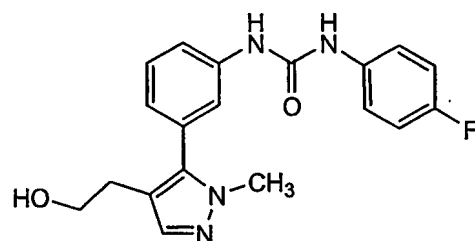


Compound 73

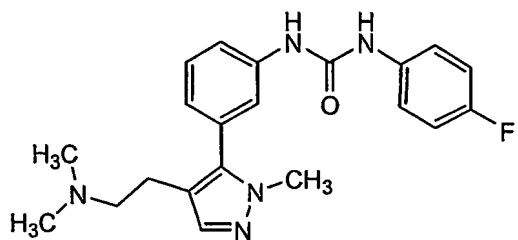
5



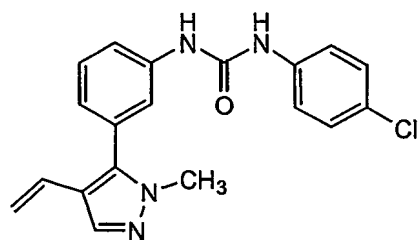
Compound 74



Compound 75

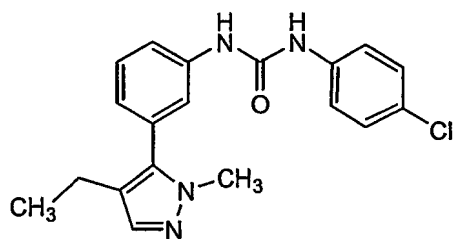


Compound 76

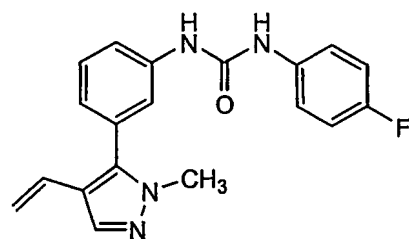


Compound 77

10



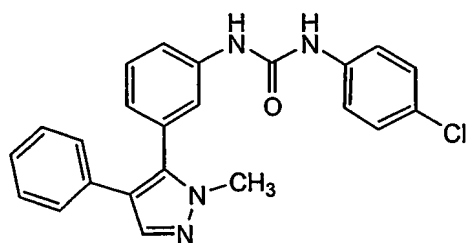
Compound 78



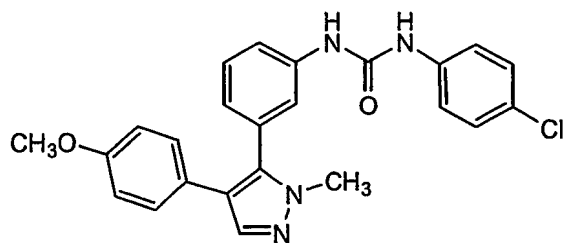
Compound 79

15

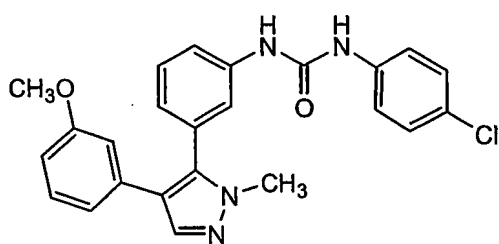
-101-



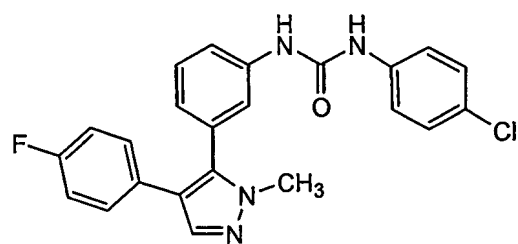
Compound 80



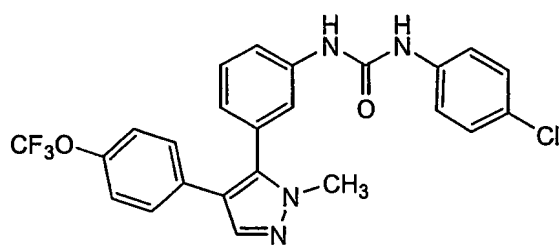
Compound 81



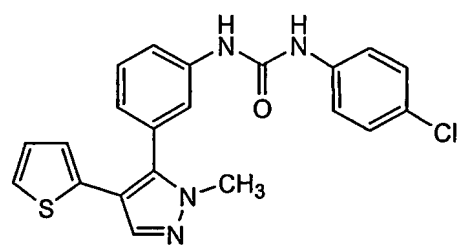
Compound 82



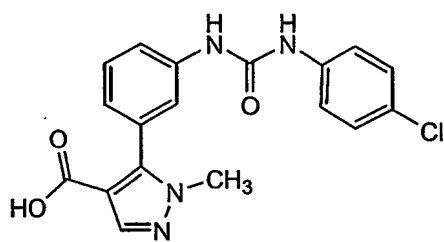
Compound 83



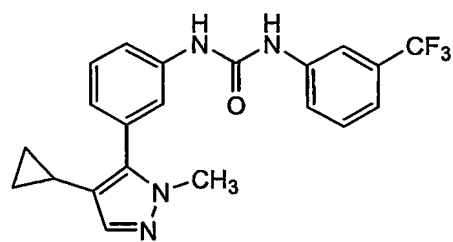
Compound 84



Compound 85



Compound 86

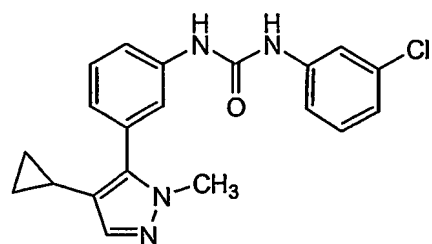


Compound 87

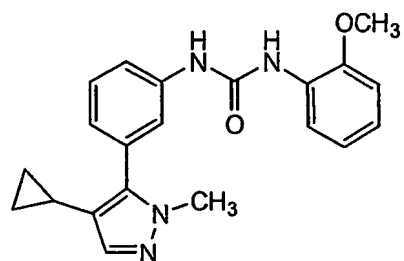
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10

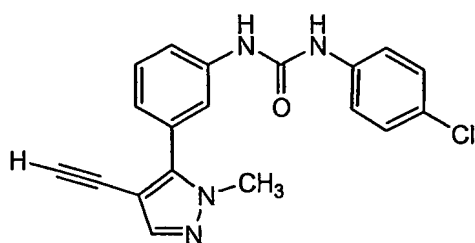
-102-



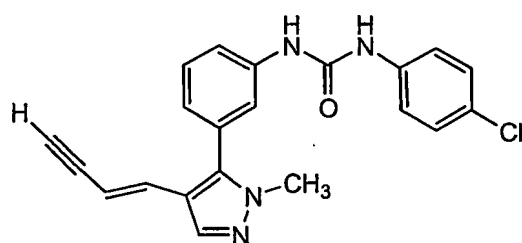
Compound 88



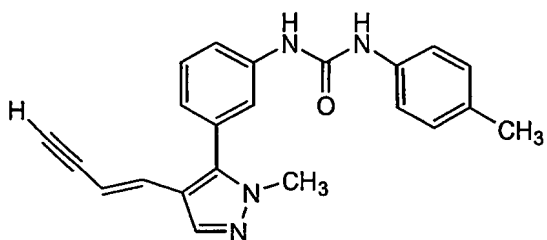
Compound 89



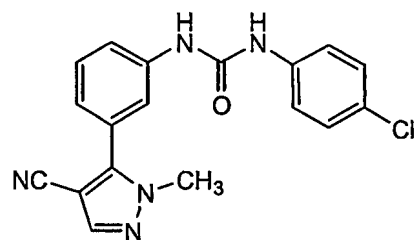
Compound 90



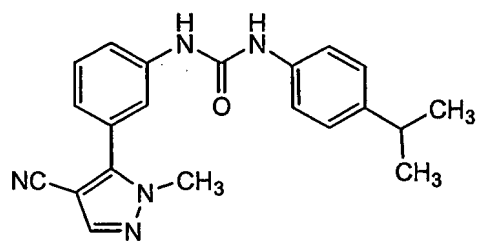
Compound 91



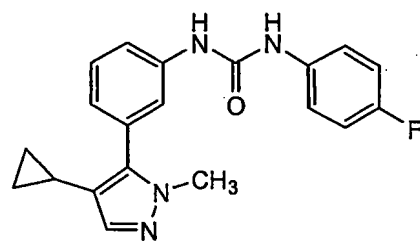
Compound 92



Compound 93



Compound 94

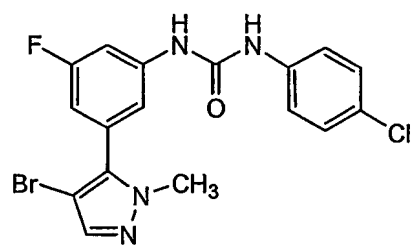


Compound 95

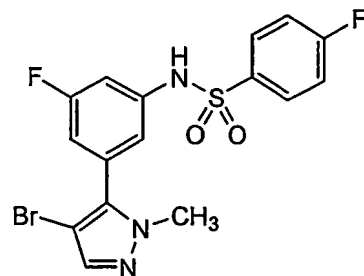
5

10

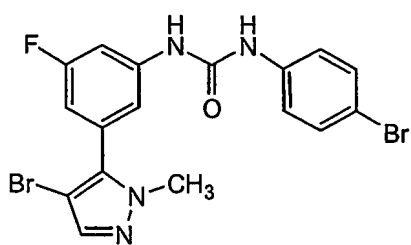
-103-



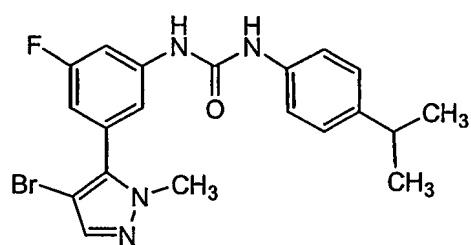
Compound 96



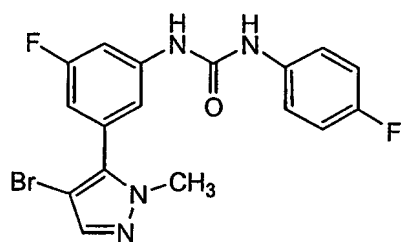
Compound 97



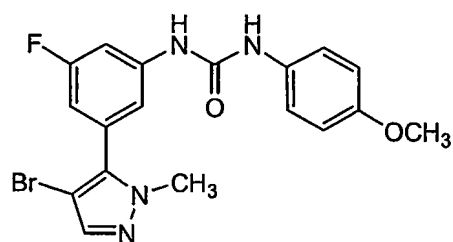
Compound 98



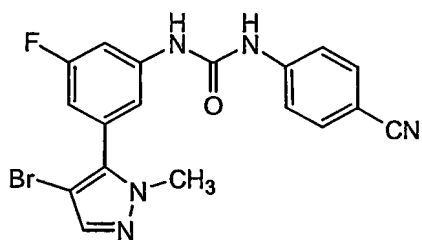
Compound 99



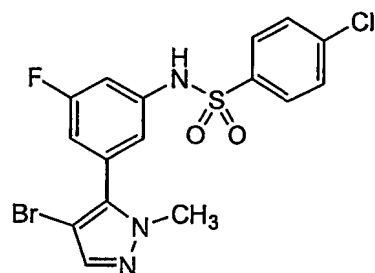
Compound 100



Compound 101



Compound 102

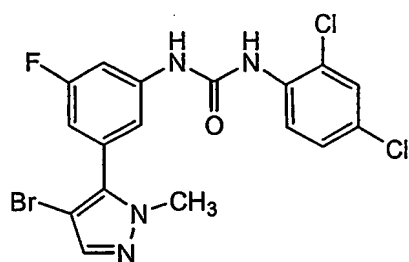


Compound 103

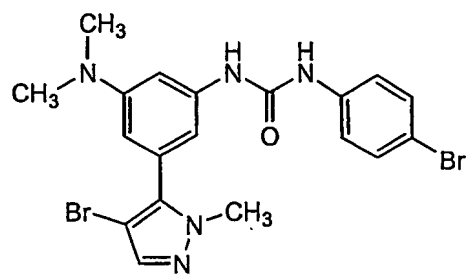
5

10

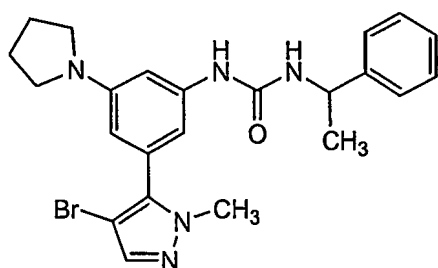
-104-



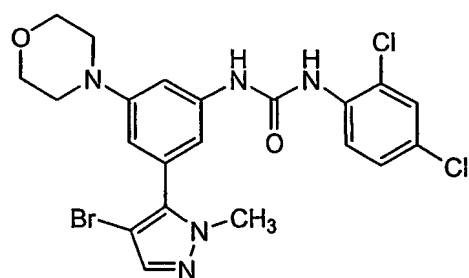
Compound 104



Compound 105

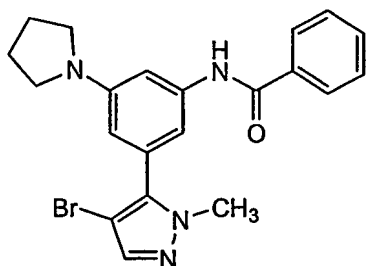


Compound 106

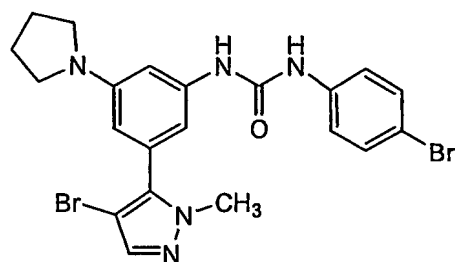


Compound 107

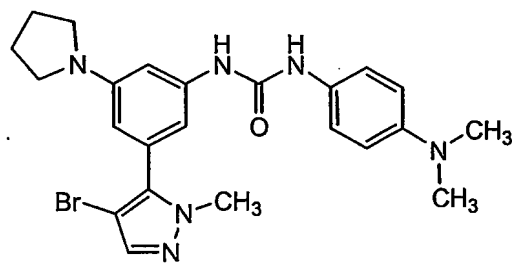
5



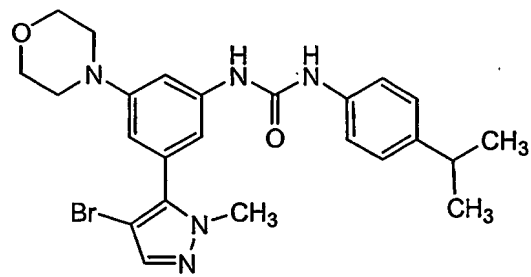
Compound 108



Compound 109



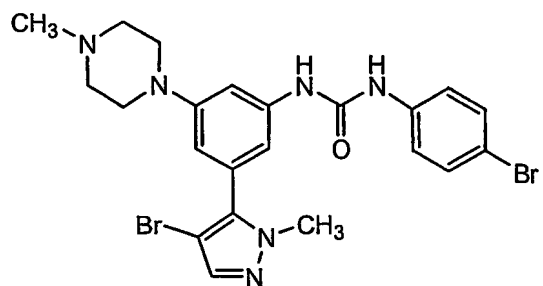
Compound 110



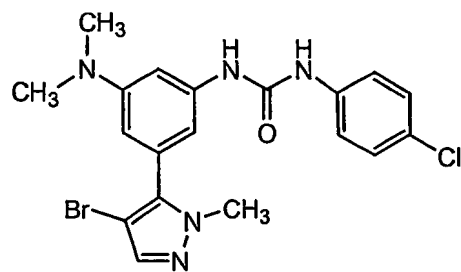
Compound 111

10

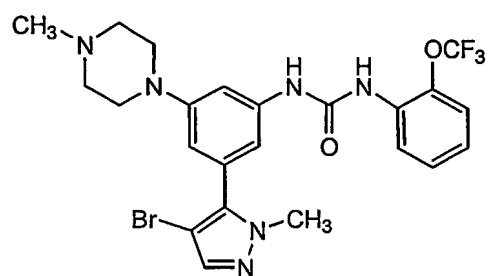
-105-



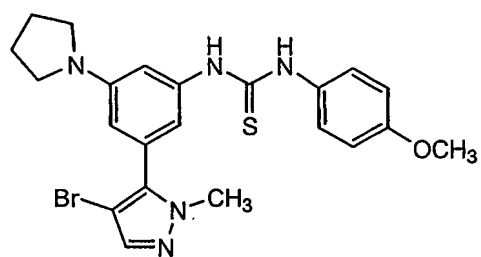
Compound 112



Compound 113

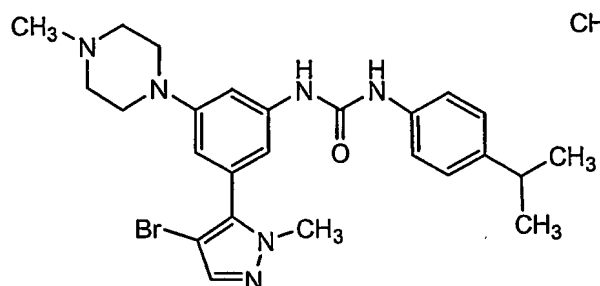


Compound 114

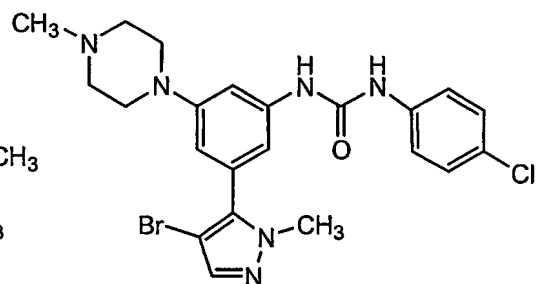


Compound 115

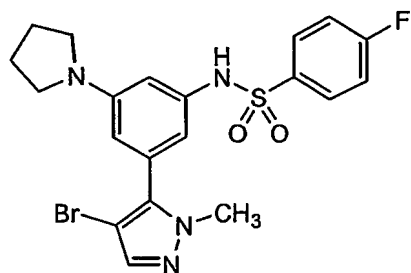
5



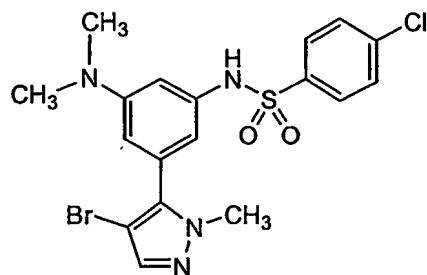
Compound 116



Compound 117



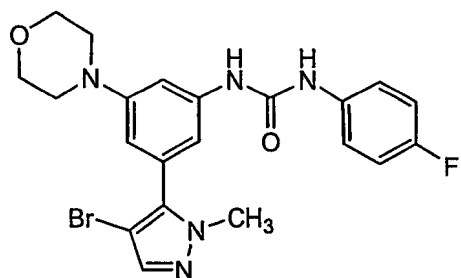
Compound 118



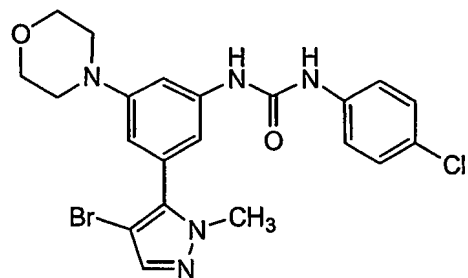
Compound 119

10

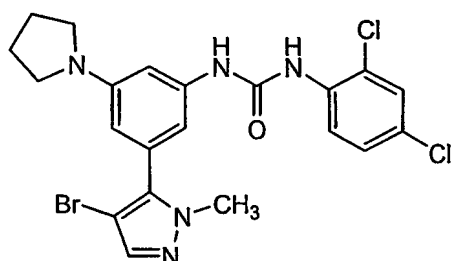
-106-



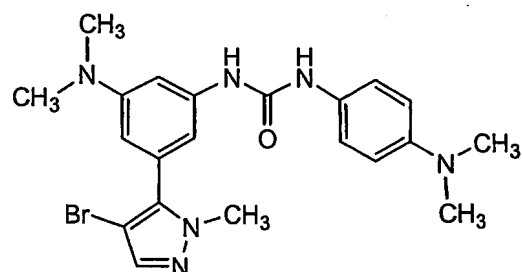
Compound 120



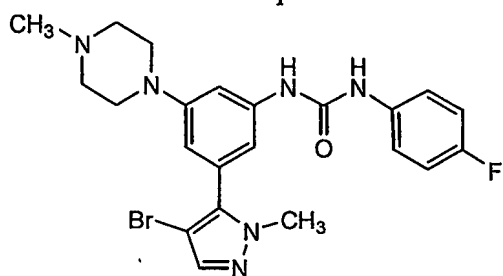
Compound 121



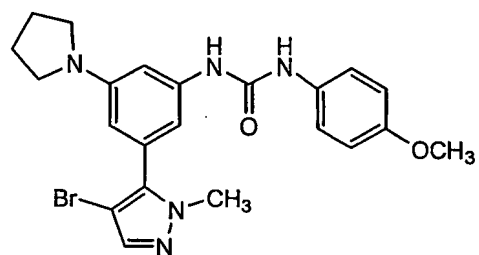
Compound 122



Compound 123

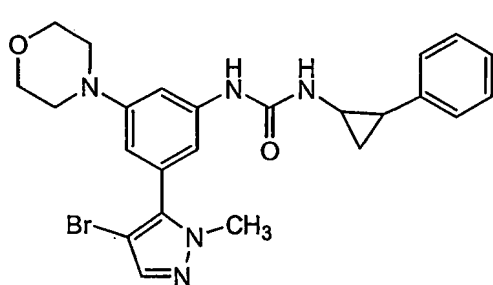


Compound 124

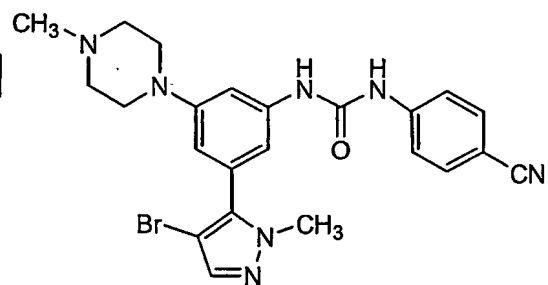


Compound 125

5



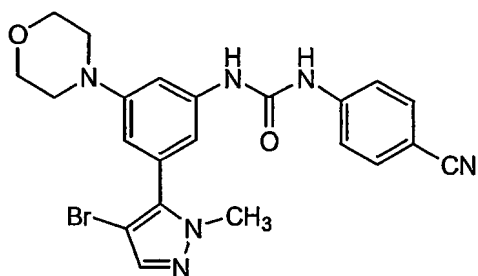
Compound 126



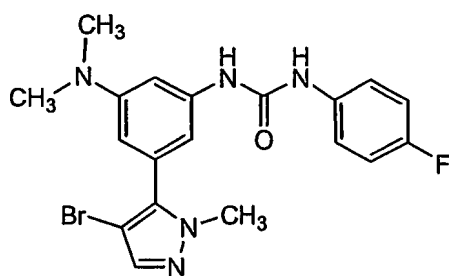
Compound 127

10

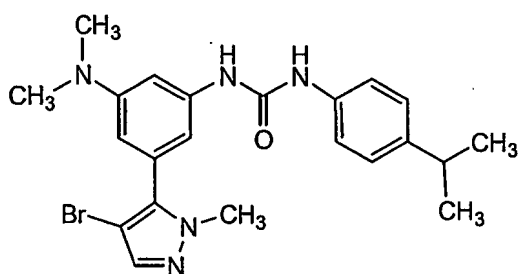
-107-



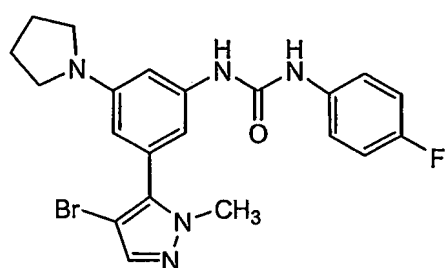
Compound 128



Compound 129

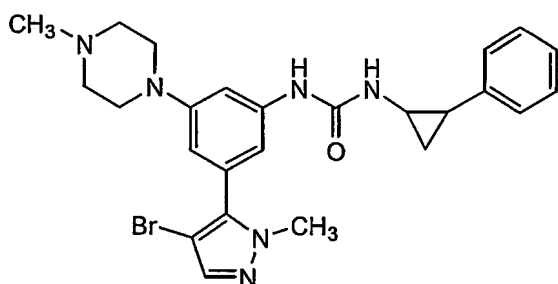


Compound 130

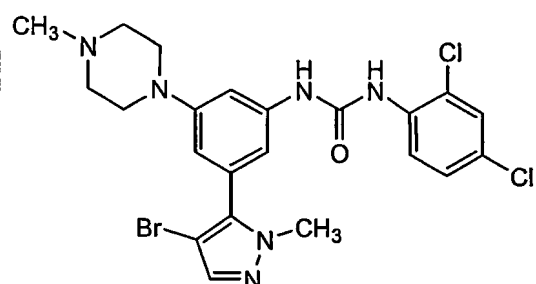


Compound 131

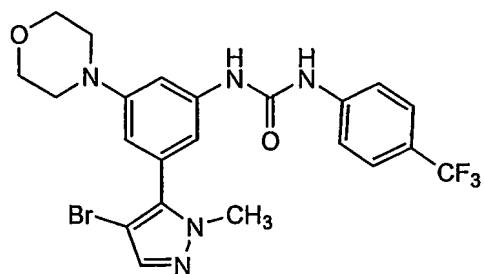
5



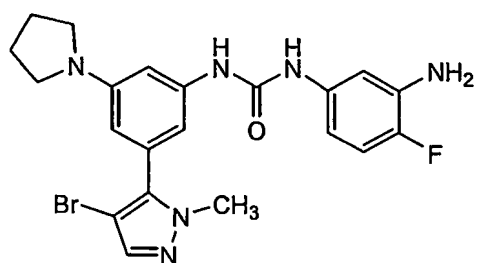
Compound 132



Compound 133



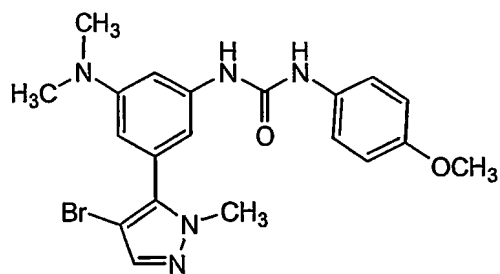
Compound 134



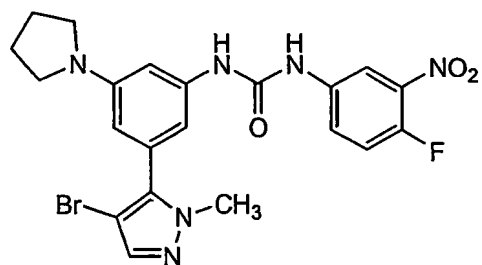
Compound 135

10

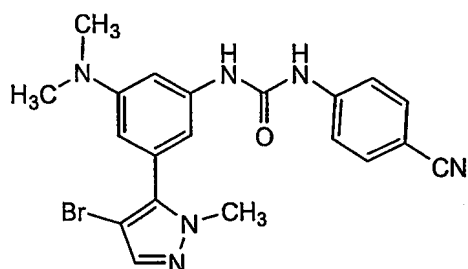
-108-



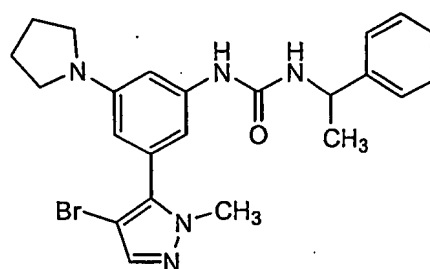
Compound 136



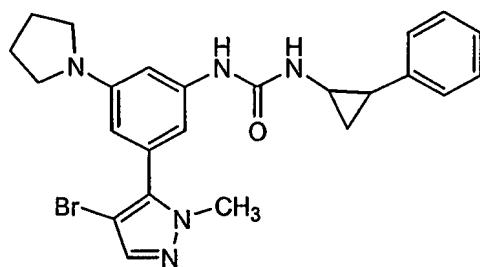
Compound 137



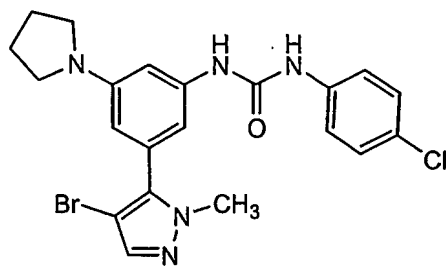
Compound 138



Compound 139

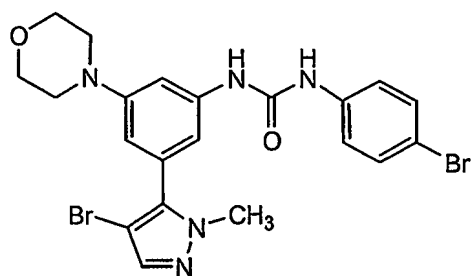


Compound 140

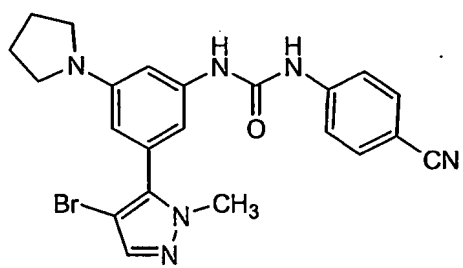


Compound 141

5



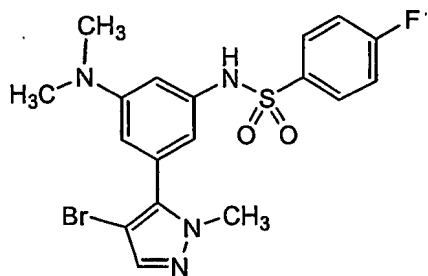
Compound 142



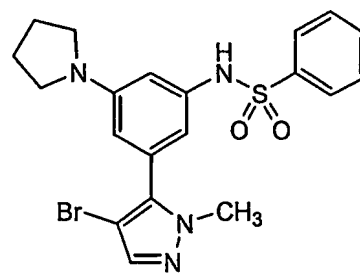
Compound 143

10

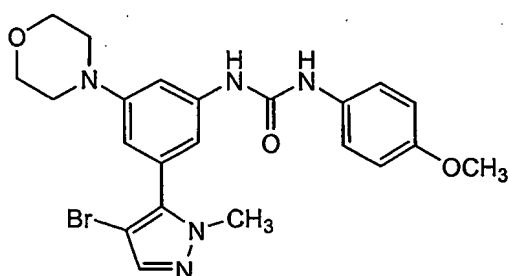
-109-



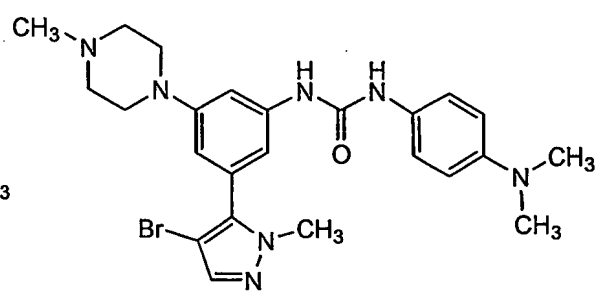
Compound 144



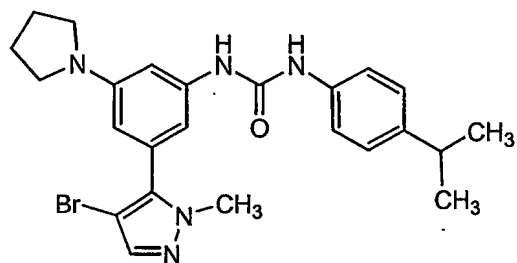
Compound 145



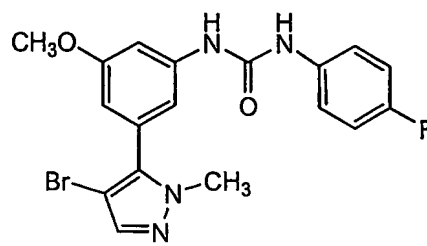
Compound 146



Compound 147

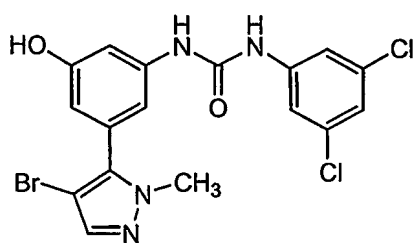


Compound 148

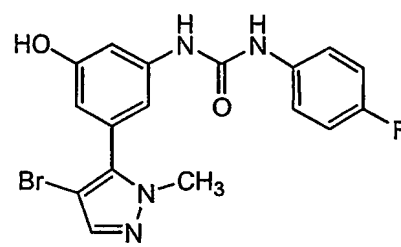


Compound 149

5

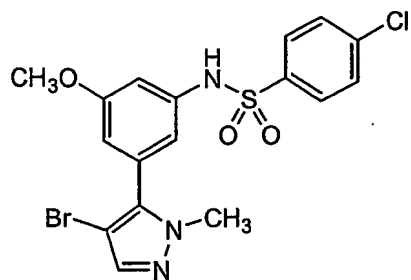


Compound 150

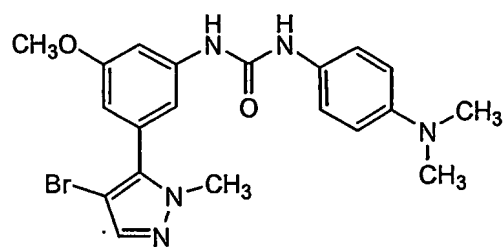


Compound 151

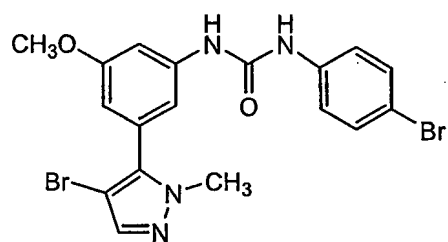
-110-



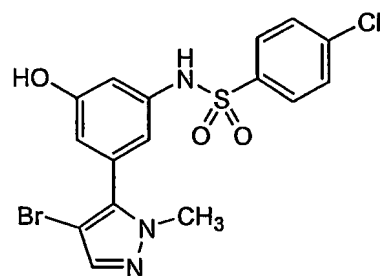
Compound 152



Compound 153

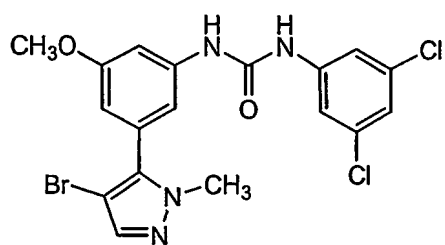


Compound 154

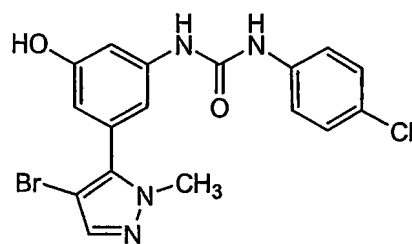


Compound 155

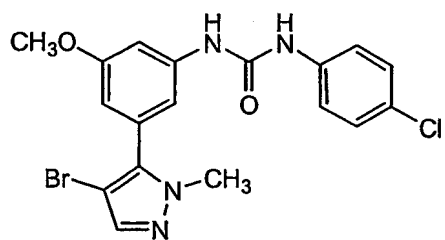
5



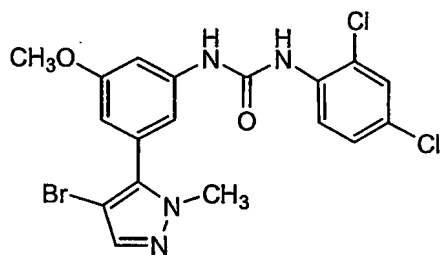
Compound 156



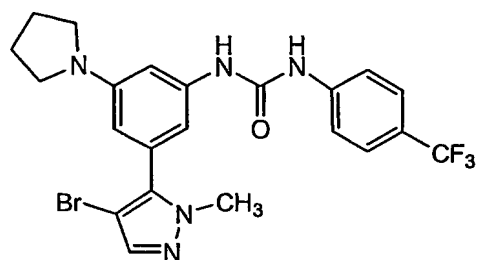
Compound 157



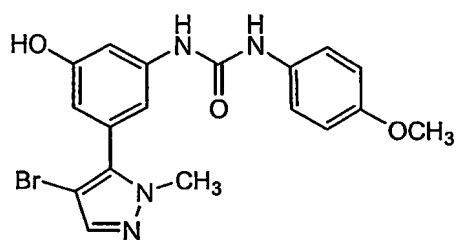
Compound 158



Compound 159



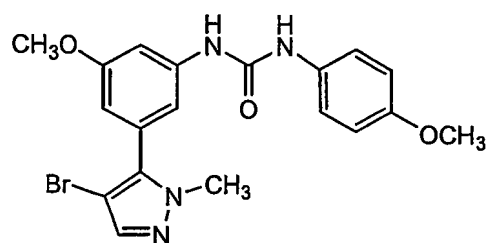
Compound 160



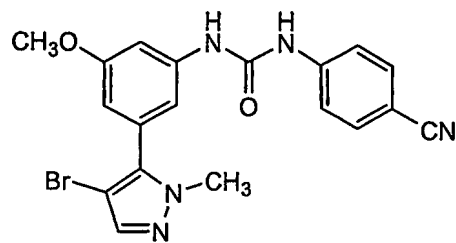
Compound 161

10

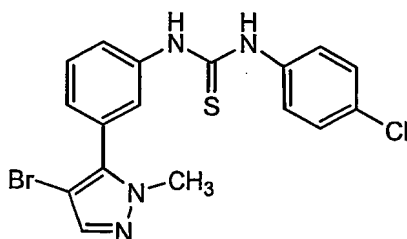
-111-



Compound 162



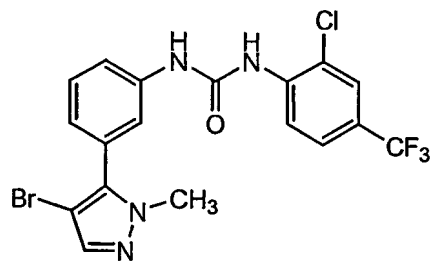
Compound 163



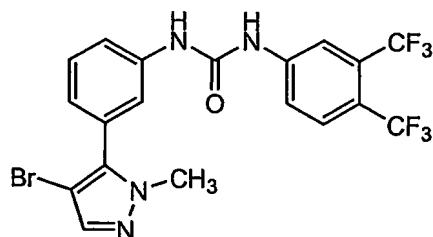
Compound 164

5

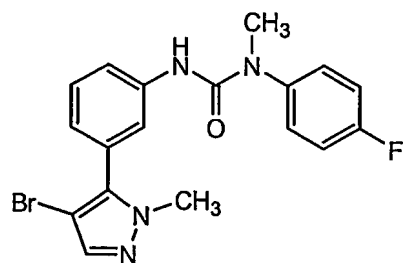
[0255] Other preferred compounds of the present invention include compounds of the following group:



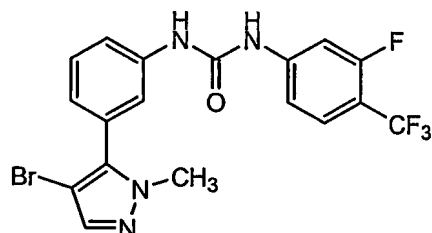
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-phenyl)-urea



1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea

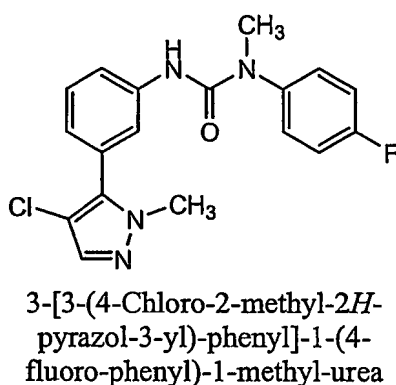
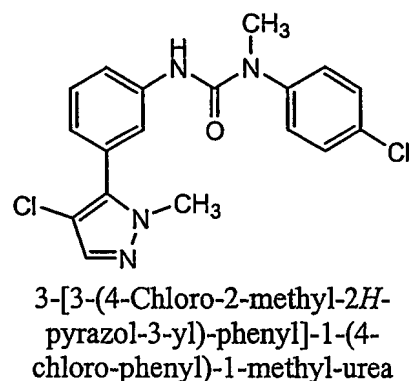
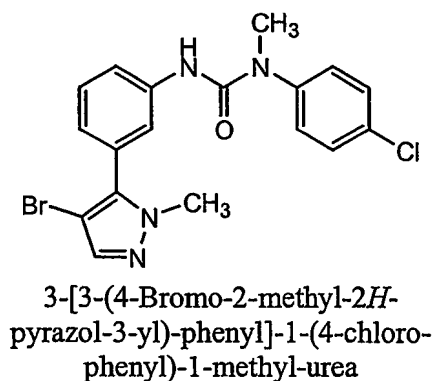


3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluorophenyl)-1-methyl-urea



1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-phenyl)-urea

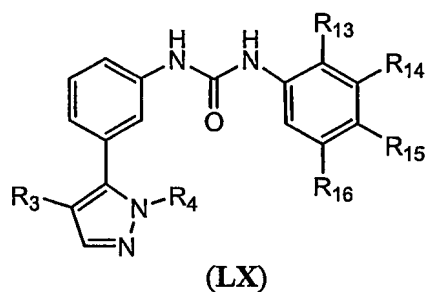
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[0256] In some embodiments of each of the genera described herein, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are included.

5 [0257] In some embodiments of each of the genera described herein, compounds of Example 13, Experiments 1-43, *infra*, and combinations or subcombinations thereof, are not included.

[0258] Still other preferred compounds falling within the scope of the general Formula (I) have the Formula LX:



10 wherein:

R₃ is Br or Cl;

R₄ is lower alkyl;

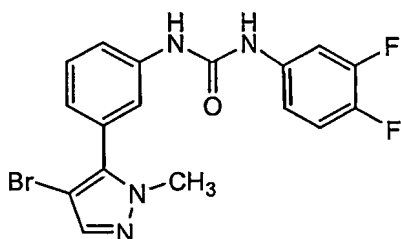
R₁₀ is H, F or CF₃;

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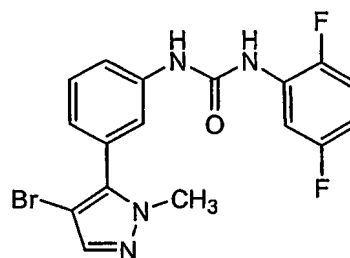
 R_{11} is H, F, Cl or CF_3 ; R_{12} is H, F or Cl; R_{13} is H or F;

and combinations and subcombinations thereof.

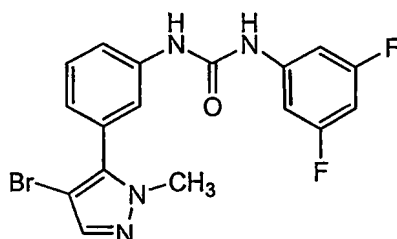
5 [0259] Specifically preferred compounds of Formula (LX) above include the following:



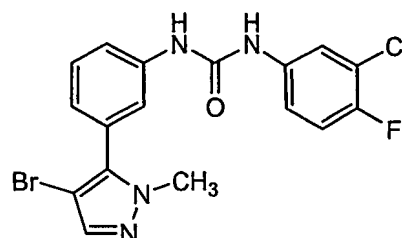
Compound 165



Compound 166

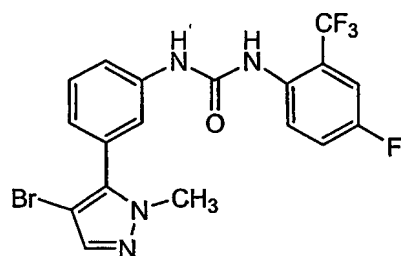


Compound 167

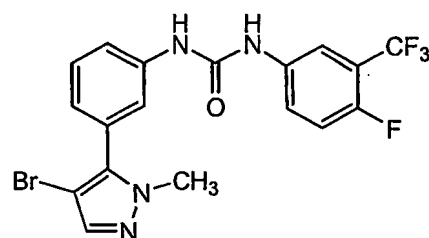


Compound 168

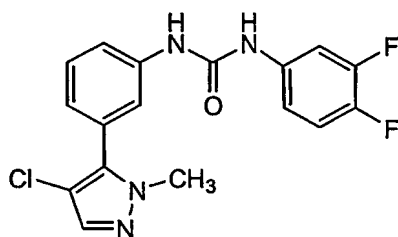
10



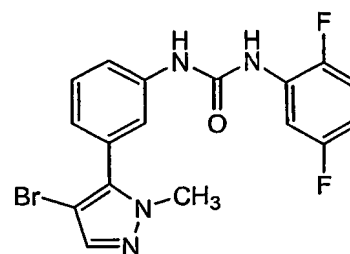
Compound 169



Compound 170

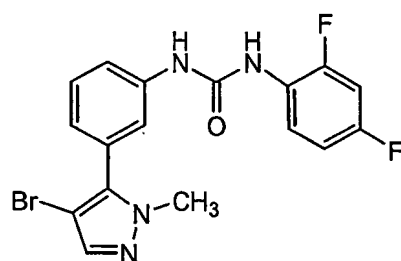


Compound 171

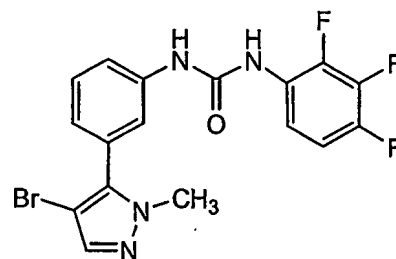


Compound 172

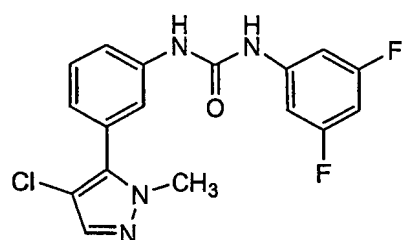
-114-



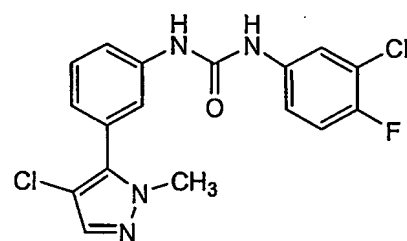
Compound 173



Compound 174

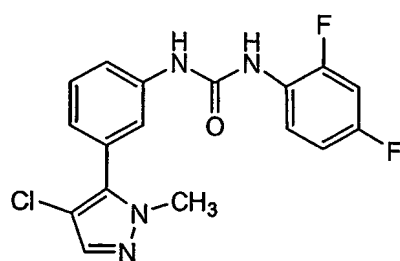


Compound 175

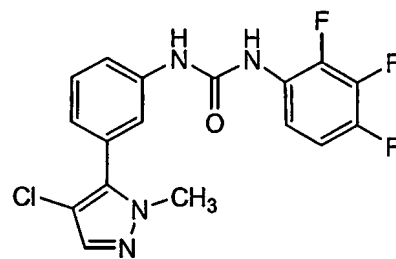


Compound 176

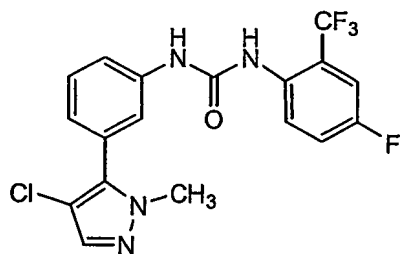
5



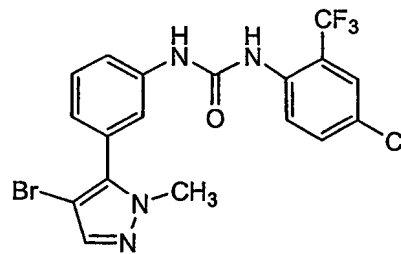
Compound 177



Compound 178

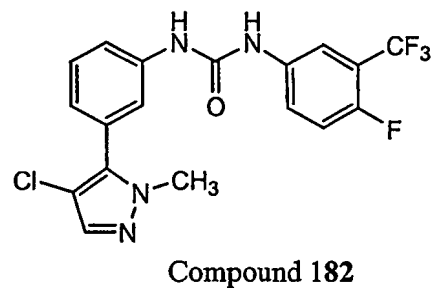
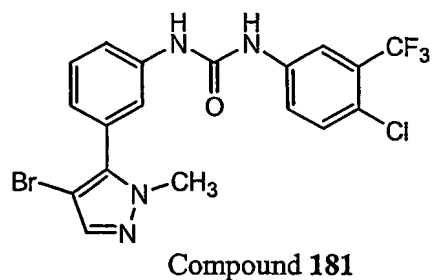


Compound 179



Compound 180

-115-



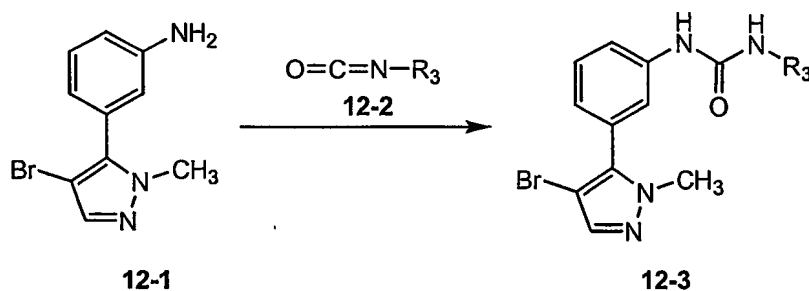
[0260] The IC_{50} values for Compounds 165-182 ranged between 8 to 158 nM in the IP_3 AP-3 assay with their corresponding values shown below:

Compound No.	5-HT _{2A} IC_{50} (nM)
165	27
166	33
167	79
168	17
169	69
170	11
171	17
172	36
173	14
174	18
175	46
176	23
177	24
178	48
179	158
180	34
181	27
182	45

EXAMPLE 12**GENERAL SYNTHETIC APPROACHES**

[0261] The compounds disclosed in this invention may be readily prepared in accordance to a variety of synthetic manipulations, all of which would be familiar to one skilled in the art.

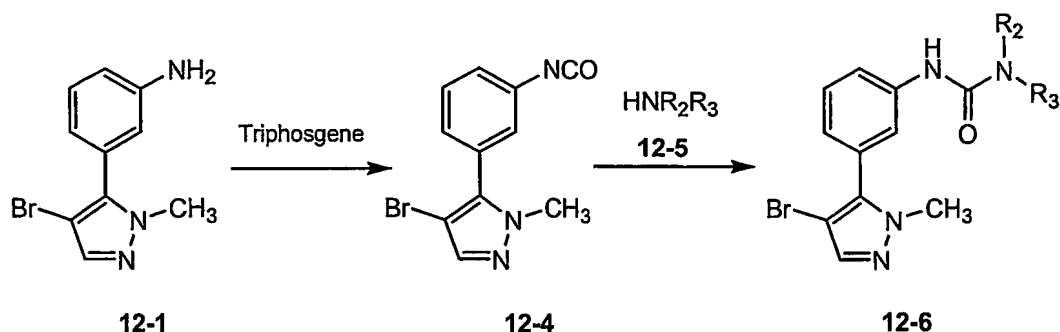
- 5 [0262] Compounds of general Formula (I) can be obtained *via* a variety of synthetic routes all of which would be familiar to one skilled in the art. The reaction of isocyanates with amines is a commonly practiced method for the formation of ureas (see Org. Syn. Coll. Vol. V, (1973), 555). Amine 12-1, 3-(4-bromo-2-methylpyrazole-3-yl)phenylamine (sold commercially as 3-(4-bromo-1-methylpyrazole-3-yl)phenylamine, by Maybridge Chemical Company, Catalog No. KM01978, CAS
10 No. 175201-77-1) reacts readily with isocyanates 12-2 in inert solvents such as halocarbons to yield the desired ureas of Formula 12-3 as shown in Scheme 12-1.



Scheme 12-1

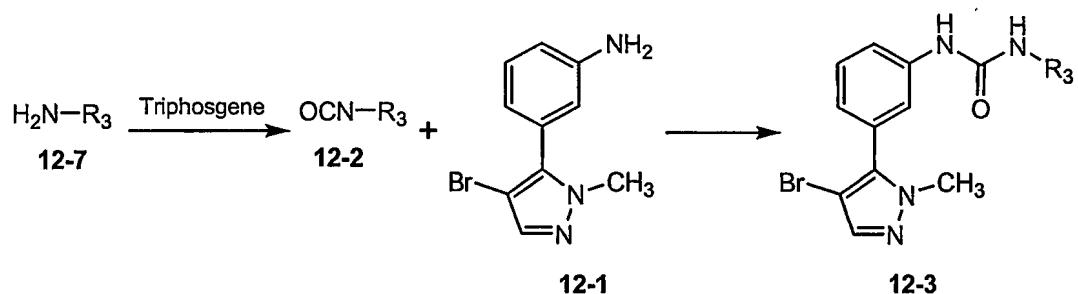
- [0263] Alternatively the amine 12-1 can be converted to the corresponding isocyanate 12-4 by the action of phosgene or a suitable phosgene equivalent, *e.g.* triphosgene, in an inert solvent such as a halocarbon in the presence of an organic base such as triethylamine (*i.e.*, TEA) or
15 diisopropylethylamine (*i.e.*, DIEA). Isocyanate 12-4 reacts with amines of the general formula 12-5 in an analogous fashion to that described above in Scheme 12-1 to give urea 12-6. This approach allows for diverse groups to be introduced for the R₂ or R₃ group based on the starting amine 12-5 (Scheme 12-2).

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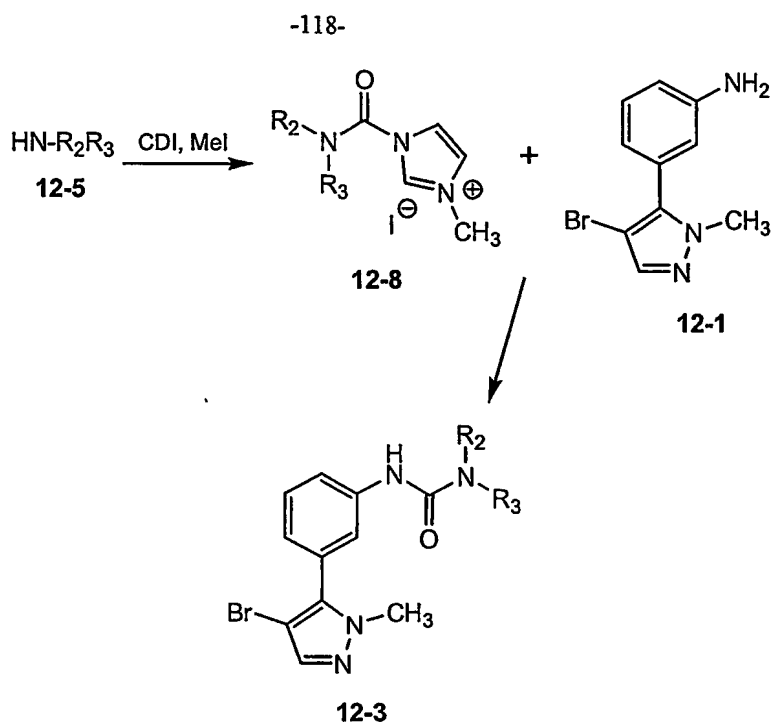
Scheme 12-2

[0264] Alternatively wherein the isocyanate of general formula 12-2 is not commercially available it can be prepared from the corresponding amine of general formula 12-7 in an analogous procedure to that described above for the preparation of 12-1. Reaction of these isocyanates with 12-1 would again yield the requisite ureas of general formula 12-3 (Scheme 12-3).



Scheme 12-3

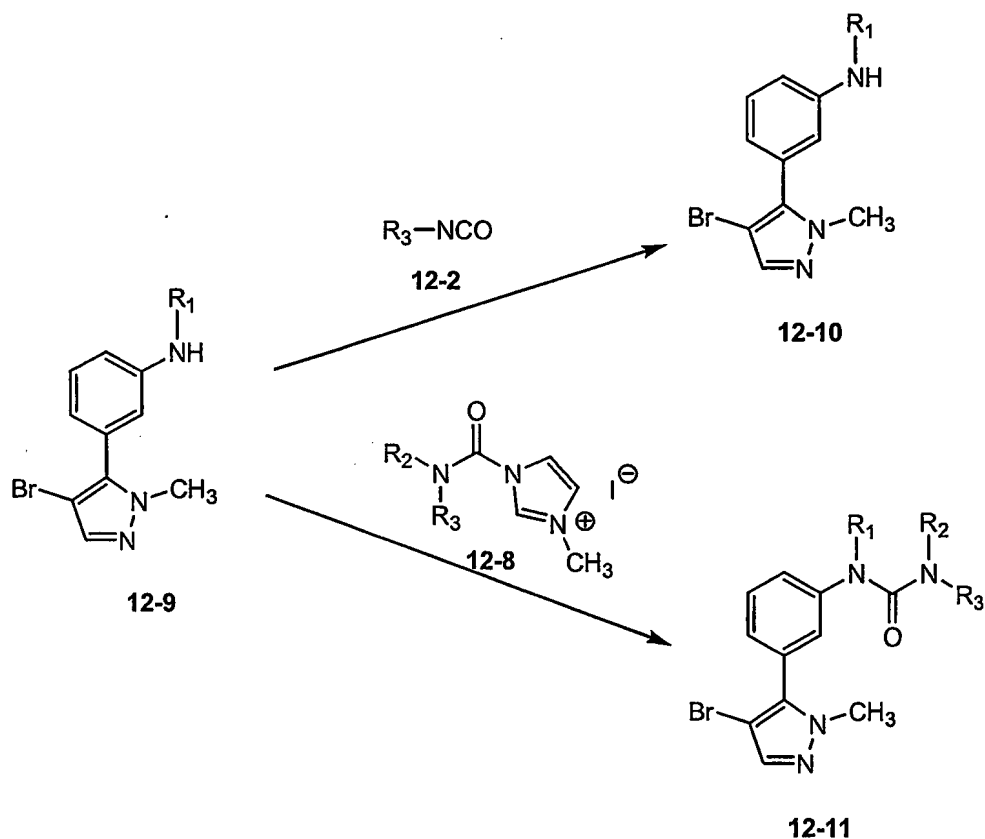
[0265] Amines of general formula 12-5 are also readily converted to activated isocyanate equivalents of general formula 12-8 by the sequential action of carbonyldiimidazole and methyl iodide in tetrahydrofuran and acetonitrile respectively (R.A. Batey *et al*, *Tetrahedron Lett.*, (1998), 39, 6267-6270.) Reaction of 12-8 with amine 12-1 in an inert solvent such as a halocarbon would yield the requisite ureas of general formula 12-3 (Scheme 12-4).



Scheme 12-4

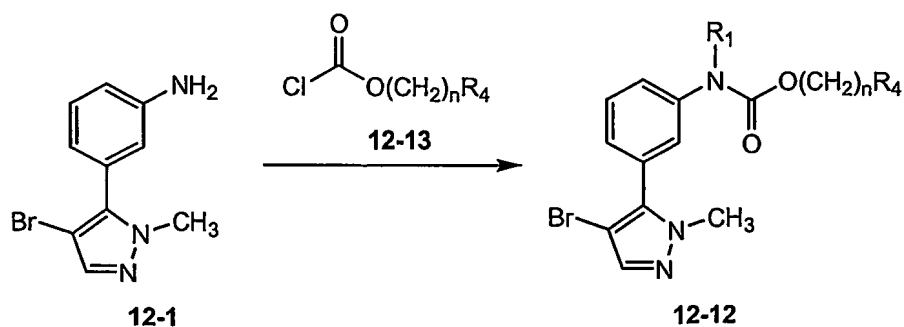
- [0266] Amine 12-1 may be monomethylated according to the procedure of J. Barluenga *et al*, *J. Chem. Soc., Chem. Commun.*, (1984), 20, 1334-1335, or alkylated according to the procedure of P. Marchini *et al*, *J. Org. Chem.*, (1975), 40(23), 3453-3456, to yield compounds of general formula 12-9 wherein R¹ = lower alkyl. Substituted amine 12-9 may be allowed to react with an isocyanate equivalent, either 12-2 or 12-8, in a similar manner as described herein to give urea 12-10 or 12-11 respectively (Scheme 12-5).

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Scheme 12-5

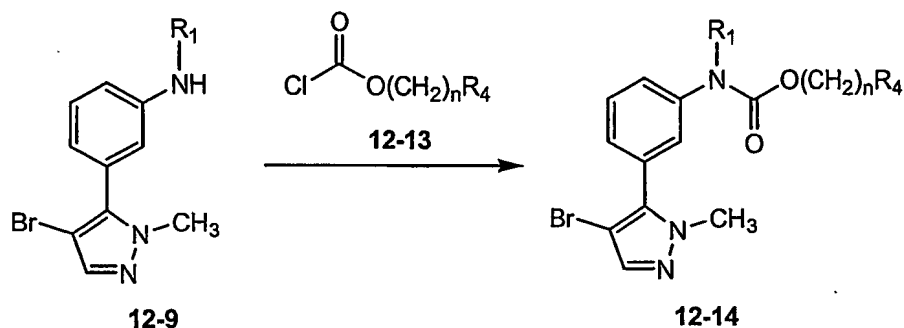
[0267] Carbamates of general formula 12-12 can be obtained in a similar manner via a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. The reaction of amine 12-1 with chloroformates (see Org. Syn. Coll. Vol. IV, (1963), 780) of general formula 12-13 in an inert solvent such as ether or halocarbon in the presence of a tertiary base such as triethylamine or ethylisopropylamine readily yields the requisite carbamates of general formula 12-12 (Scheme 12-6).



Scheme 12-6

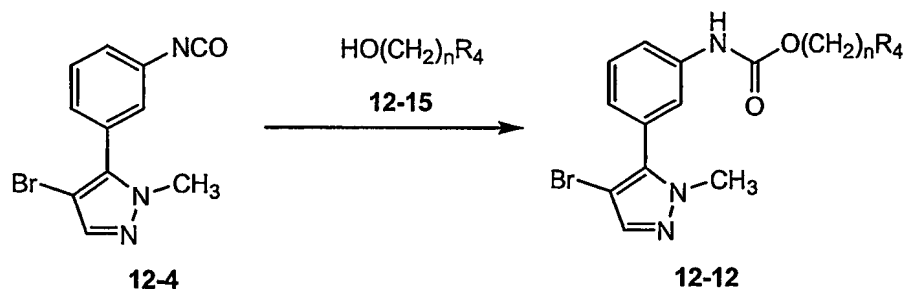
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[0268] Analogously, amines of general formula 12-9 react similarly with chloroformates 12-13 to yield the requisite carbamates of the general formula 12-14 (Scheme 12-7).



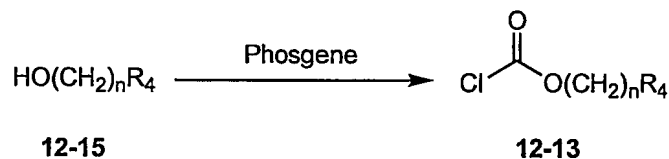
Scheme 12-7

5 [0269] An alternate route employs the ready reaction of an alcohol with an isocyanate. Thus isocyanate 12-4 described previously reacts readily with alcohols 12-15 in an aprotic solvent such as ether or chlorocarbon to yield the desired carbamates of general formula 12-12 (Scheme 12-8) :



Scheme 12-8

[0270] Chloroformates of general formula 12-13 not commercially available may be readily prepared from the corresponding alcohol 12-15 in an inert solvent such as toluene, chlorocarbon or ether by the action of excess phosgene (see Org. Syn. Coll. Vol. III, (1955), 167) (Scheme 12-9).

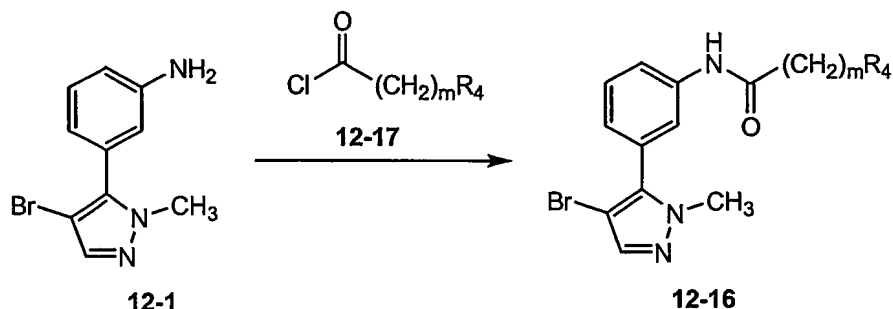


Scheme 12-9

[0271] Amide compounds of the general formula 12-16 can be obtained via a variety of synthetic manipulations, all of which would be familiar to one skilled in the art. The reaction of amine

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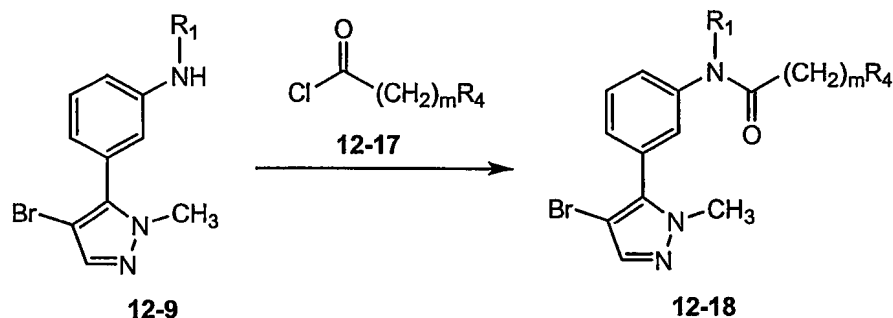
12-1 with acid chlorides (see Org. Syn. Coll. V, (1973), 336) of general formula **12-17** to yield the desired amides **12-16** is readily achieved in an inert solvent such as chloroform or dichloromethane in the presence of an organic base such as triethylamine or ethyldiisopropylamine (Scheme 12-10).



5

Scheme 12-10

[0272] In an identical fashion amines of general formula **12-9** would react with acid chlorides **12-17** to yield the desired amides **12-18** (Scheme 12-11).

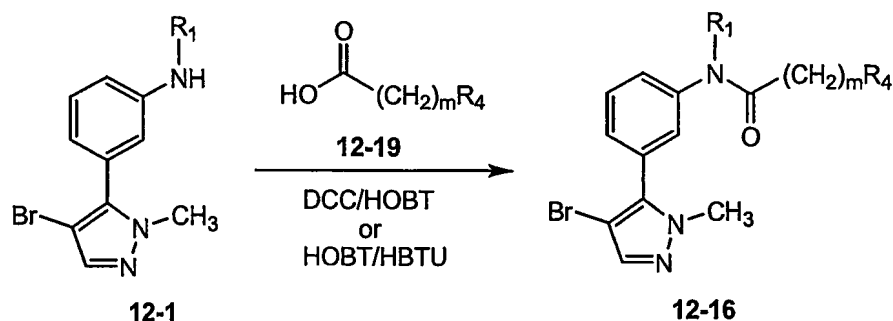


Scheme 12-11

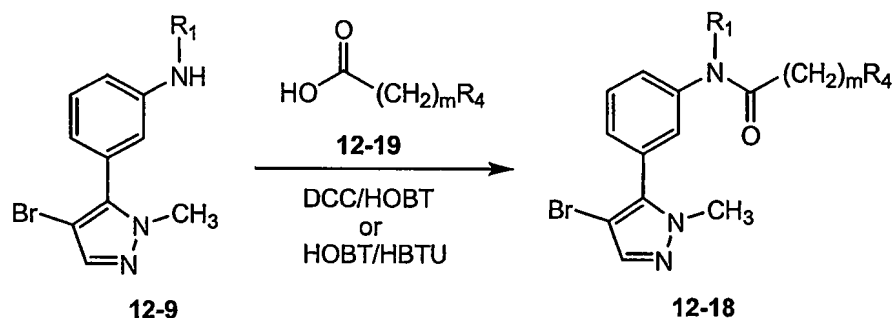
[0273] Alternatively the corresponding acids of general formula **12-19** may be coupled with dicyclohexylcarbodiimide (DCC)/hydroxybenzotriazole (HOBt) (see W. König et al, Chem. Ber., (1970), 103, 788) or hydroxybenzotriazole (HOBt)/2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (see M. Bernatowicz et al., Tetrahedron Lett., (1989), 30, 4645) as condensing agents in dimethylformamide or chloroform with amines **12-1** and **12-9** respectively to give amides **12-16** (Schemes 12-12) and **12-18** (Scheme 12-13) respectively as described above.

15

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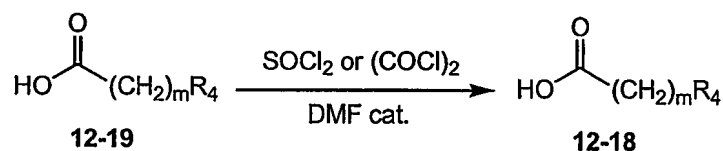


Scheme 12-12



Scheme 12-13

[0274] The acids of general formula **12-18** are readily converted to the corresponding acid chlorides **12-19** by the action of thionyl chloride or oxalyl chloride in the presence of catalytic dimethylformamide:



Scheme 12-14

[0275] A third aspect of the present invention provides a compound of Formula (I) or a solvate or physiologically functional derivative thereof for use as a therapeutic agent, specifically as a modifier of the activity of the serotonin 5-HT_{2A} receptor. Modifiers of the activity of the serotonin 5-HT_{2A} receptor are believed to be of potential use for the treatment or prophylaxis of CNS, gastrointestinal, cardiovascular, and inflammatory disorders. Compounds of the Formula (I) may be administered by oral, sublingual, parenteral, rectal, or topical administration. In addition to the neutral

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forms of compounds of Formula (I) by appropriate addition of an ionizable substituent, which does not alter the receptor specificity of the compound, physiologically acceptable salts of the compounds may also be formed and used as therapeutic agents. Different amounts of the compounds of Formula (I) will be required to achieve the desired biological effect. The amount will depend on factors such as the specific compound, the use for which it is intended, the means of administration, and the condition of the treated individual. A typical dose may be expected to fall in the range of 0.001 to 200 mg per kilogram of body weight of the treated individual. Unit does may contain from 1 to 200 mg of the compounds of Formula (I) and may be administered one or more times a day, individually or in multiples. In the case of the salt or solvate of a compound of Formulas (I), the dose is based on the cation (for salts) or the unsolvated compound.

[0276] A fourth aspect of the present invention provides pharmaceutical compositions, comprising at least one compound of Formula (I) and/or an acceptable salt or solvate thereof (*e.g.*, a pharmaceutically acceptable salt or solvate) as an active ingredient combined with at least one carrier or excipient (*e.g.*, pharmaceutical carrier or excipient). Pharmaceutical compositions may be used in the treatment of clinical conditions for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated, particularly where the active ingredient is preferentially selective for the 5-HT_{2A} receptor over the 5-HT_{2A} receptor, and most particularly where the active ingredient is also an inverse agonist at the 5-HT_{2A} receptor. At least one compound of Formula (I) may be combined with the carrier in either solid or liquid form in a unit dose formulation. The pharmaceutical carrier must be compatible with the other ingredients in the composition and must be tolerated by the individual recipient. Other physiologically active ingredients may be incorporated into the pharmaceutical composition of the invention if desired, and if such ingredients are compatible with the other ingredients in the composition. Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

[0277] Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing

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the solution before filling and sealing an appropriate vial or ampoule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

[0278] The fifth aspect of the present invention provides for the use of a compound of formula (I) in the preparation of a medicament for the treatment of a medical condition for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated.

[0279] The sixth aspect of the present invention provides for a method of treatment of a clinical condition of a mammal, such as a human, for which a modifier of the activity of the serotonin 5-HT_{2A} receptor is indicated, which comprises the administration to the mammal of a therapeutically effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof.

EXPERIMENTAL DATA

EXAMPLE 13

Preparation and Analysis of Compounds

Experiments 13.1 – 13.43

[0280] Mass spectra were recorded on a Micromass Platform™ LC with Gilson HPLC. Infra-red spectra were recorded on a Nicolet Avatar™ 360 FT-IR. Melting points were recorded on a Electrothermal IA9200™ apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Bruker™ 300MHz machine. Chemical shifts are given with respect to tetramethylsilane. In the text the following abbreviations are used; s (singlet), d (doublet), t (triplet), m (multiplet) or combinations thereof. Chemical shifts are quoted in parts per million (ppm) and with coupling constants in Hertz.

[0281] Thin layer chromatography was carried out using aluminium backed silica plates (250μL; GF₂₅₄). HPLC was recorded either on a HP Chemstation™ 1100 HPLC using a Hichrom 3.5 C18 reverse phase column (50mm x 2.1mm i.d.). Linear gradient elution over 5 minutes – 95% water (+0.1% TFA) / 5% acetonitrile (+0.05% TFA) down to 5% water / 95% acetonitrile. Flow rate 0.8mL/min (Method A); or on a Hichrom 3.5 C18 reverse phase column (100mm x 3.2mm i.d.). Linear gradient elution over 11 minutes – 95% water (+0.1% TFA) / 5% acetonitrile (+0.05% TFA) down to 5% water / 95% acetonitrile. Flow rate 1mL/min (Method B). Samples were routinely monitored at 254nm unless otherwise stated.

[0282] All reagents were purchased from commercial sources.

Experiment 13.1**Preparation and Analysis of Compound 1**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide

[0283] To 4-methoxyphenylchloroformate (19 mg, 0.10 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (25 mg, 0.10 mmol) and triethylamine (14 μ L, 0.10 mmol) in CH₂Cl₂ (0.5 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica (40% EtOAc/hexane) gave the title compound as a colourless solid (21 mg, 52%), m.p. 140.3-141.8°C. (EtOAc/hexane).

IR: ν_{\max} = 1748, 1592, 1504, 1412, 1190, 835, 764, 676 cm⁻¹ MS (ES⁺): m/z (%) = 404 (M+H ⁸¹Br, 100), 402 (M+H ⁷⁹Br, 90).

¹H-NMR (CD₃ OD): δ = 3.80 (3H, s, CH₃), 3.81 (3H, s, CH₃), 6.91-6.98 (2H, m, ArH), 7.07-7.18 (3H, m, ArH), 7.42-7.53 (4H, m, ArH).

[0284] HPLC: retention time 3.28 mins (Method A). Tlc: R_f 0.4 (EtOAc/hexane).

Experiment 13.2**Preparation and Analysis of Compound 2**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide

[0285] To thiophene-2-carbonyl chloride (11 μ L, 0.09 mmol) in CH₂Cl₂ (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (25 mg, 0.09 mmol) and triethylamine (14 μ L, 0.09 mmol) in CH₂Cl₂ (0.5 mL). The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (24 mg, 68%), m.p. 127.8-128.6°C (EtOAc/hexane). :

MS (ES⁺): m/z (%) = 364 (M+H ⁸¹Br, 96), 362 (M+H ⁷⁹Br, 100).

¹H-NMR (CD₃ OD): δ = 3.81 (3H, s, CH₃), 7.19 (2H, m, ArH), 7.48-7.58 (2H, m, ArH), 7.68-7.83 (3H, m, ArH), 7.93 (1H, dd, J=1.0, 3.8, ArH).

[0286] HPLC: retention time 3.12 min (Method A). TLC: R_f 0.30 (30% EtOAc/hexane).

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Experiment 13.3**Preparation and Analysis of Compound 7**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl) amino)carboxamide

[0287] This compound is commercially available from Maybridge Chemical Company,
5 Catalog No. KM04515, under the name N-(3-(4-bromo-1-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl) amino)carboxamide. :

Experiment 13.4**Preparation and Analysis of Compound 10**

10 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl)methyl)amino)carboxamide

[0288] To a stirred solution of triphosgene (12 mg, 0.04 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (33 μ L, 0.24 mmol) in CH₂Cl₂ (0.5 mL). After 1 h, 4- (trifluoromethoxy)benzylamine
15 (23 mg, 0.12 mmol) was added. The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (75% EtOAc/hexane) gave the title compound as a colourless solid (38 mg, 68%), m.p. 144.6-145.8 °C (EtOAc/hexane).

IR: ν_{\max} = 1626, 1558, 1278, 1160, 969, 871, 789, 703 cm⁻¹ MS (ES⁺): m/z (%) = 471 (M+H ⁸¹Br, 91), 469 (M+H ⁷⁹Br, 100).

20 ¹H-NMR (CD₃ OD): δ = 3.81 (3H, s, CH₃), 4.42 (2H, s, CH₂), 7.06 (1H, d, J=7.1, ArH), 7.24 (2H, d, J=8.4, ArH), 7.37-7.52 (6H, m, ArH).

[0289] HPLC: retention time 3.06 mins (Method A). Tlc: R_f 0.5 (EtOAc).

Experiment 13.5**25 Preparation and Analysis of Compound 39**

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide

[0290] To di-tert-butyl dicarbonate (36 mg, 0.17 mmol) in methanol (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (42 mg, 0.17 mmol) in methanol (1 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica
30 (40% EtOAc/hexane) gave the title compound as a colourless solid (29 mg, 49%) (EtOAc/hexane).

MS (CI⁻): m/z (%) = 352 (M-H ⁸¹Br, 100), 350 (M-H ⁷⁹Br, 96).

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¹H-NMR (DMSO d₆): δ = 1.46 (9H, s, 3.times. CH₃), 3.73 (3H, s, CH₃), 7.07 (1H, m, ArH), 7.42 (1H, t, J=7.7, ArH), 7.53-7.60 (2H, m, ArH), 7.64 (1H, s, ArH), 9.57 (1H, s, NH).

[0291] HPLC: retention time 7.15 min (Method B).

5 Experiment 13.6

Preparation and Analysis of Compound 40

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl)carboxamide

[0292] To 4-(trifluoromethoxy)benzoyl chloride (19 μL, 0.12 mmol) in CH₂Cl₂ (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (17 μL, 0.12 mmol) in CH₂Cl₂ (0.5 mL). The reaction mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (40 mg, 76%), m.p. 138.6-139.6°C (EtOAc/hexane).

MS (ES⁺): m/z (%)=442 (M+H ⁸¹Br, 93), 440 (M+H ⁷⁹Br, 100).

¹H-NMR (DMSO d₆): δ=3.79 (3H, s, CH₃), 7.27 (1H, m, ArH), 7.45-7.60 (3H, m, ArH), 7.65 (1H, s, ArH), 7.87 (2H, m, ArH), 8.09 (2H, m, ArH), 10.51 (1H, s, NH).

[0293] HPLC: retention time 3.60 min (Method A). TLC: R_f 0.40 (50% EtOAc/hexane).

Experiment 13.7

Preparation and Analysis of Compound 41

20 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl)carboxamide

[0294] To 4-chlorobenzoyl chloride (15 mg, 0.08 mmol) in CH₂Cl₂ (1 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (21 mg, 0.08 mmol) and triethylamine (12 μL, 0.08 mmol) in CH₂Cl₂ (0.5 mL). The mixture was stirred for 16 h and concentrated. Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (23 mg, 72%), m.p. 184.4-184.8 °C (EtOAc/hexane).

MS (ES⁺): m/z (%)=394 (M+H ⁸¹Br ³⁷Cl, 34), 392 (M+H ⁷⁹Br ³⁷Cl (⁸¹Br ³⁵Cl), 100), 390 (M+H ⁷⁹Br ³⁵Cl, 67).

¹H-NMR (DMSO d₆): δ = 3.79 (3H, s, CH₃), 7.25 (1H, d, J=7.9, ArH), 7.51-7.6 (3H, m, ArH), 7.69 (1H, s, ArH), 7.90 (2H, m, ArH), 8.00 (2H, m, ArH), 10.51 (1H, s, NH).

30 [0295] HPLC: retention time 3.40 min (Method A). TLC: R_f 0.35 (50% EtOAc/hexane).

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Experiment 13.8**Preparation and Analysis of Compound 42**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)acetamide

- [0296] A solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (35 mg, 0.14 mmol) and triethylamine (23 μ L, 0.17 mmol) in DMF (0.5 mL) was added in one portion to a stirred solution of 4-trifluoromethoxyphenylacetic acid (31 mg, 0.14 mmol), HBTU (53 mg, 0.14 mmol) and HOBT (19 mg, 0.14 mmol) in DMF (1 mL). The mixture was heated at 70 °C for 24 h and then quenched with aqueous sodium bicarbonate solution. Ethyl acetate was added and the organic phase separated, washed with water (.times.3), brine, dried (MgSO₄) and evaporated.
- 10 [0297] Chromatography on flash silica (50% EtOAc/hexane) gave the title compound as a colourless solid (43 mg, 68%). m.p. 141.2-142.5 °C (EtOAc/hexane).
IR: ν_{max} = 1684, 1592, 1510, 1253, 1217, 1157, 987, 798, 700 cm^{-1} .
MS (ES⁺): m/z (%) = 456 (M+H ⁸¹Br, 100), 454 (M+H ⁷⁹Br, 94).
¹H-NMR (DMSO d₆): δ = 3.72 (2H, s, CH₂), 3.75 (3H, s, CH₃), 7.17 (1H, d, J=7.7, ArH), 7.33 (2H, d, J=8.7, ArH), 7.38-7.51 (3H, m, ArH), 7.62-7.73 (3H, m, ArH), 10.44 (1H, s, NH).
- 15 [0298] HPLC: retention time 3.52 min (Method A).

Experiment 13.9**Preparation and Analysis of Compound 43**

- 20 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl)acetamide
- [0299] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 3-fluorophenylacetic acid (18 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (12 mg, 26%). R_f 0.41 (ethyl acetate-toluene, 1:1).
- 25 MS (AP⁺): m/z (%) = 390 (M-H ⁸¹Br 100), 388 (M-H ⁷⁹Br, 100).
¹H-NMR (CDCl₃): δ = 3.77 (2H, s), 3.83 (3H, s), 7.02-7.20 (4H, m), 7.54 (1H, s), 7.60-7.63 (1H, m).
- 30 [0300] HPLC (Method B): retention time 7.07 min (100%).

Experiment 13.10**Preparation and Analysis of Compound 44**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl)acetamide

- 5 [0301] A solution of 3-methoxyphenylacetyl chloride (0.02 ml, 0.12 mmol) in dichloromethane (0.75ml) was added dropwise at 0 °C to a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol) and triethylamine (0.02 ml, 0.13 mmol) in dichloromethane (0.75 ml). The resulting mixture was stirred at room temperature for 16 h and then poured into brine. The organic layer was washed with more brine then dried over magnesium sulphate and concentrated in
10 vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (9 mg, 19%). Rf 0.30 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=402 (M+H ⁸¹Br, 100), 400 (M+H ⁷⁹Br, 95).

¹H-NMR (CDCl₃): δ = 3.76 (2H, s), 3.82 (3H, s), 3.85 (3H, s), 6.84-6.90 (3H, m),
7.07-7.44 (5H, m), 7.53 (1H, s), 7.60 (1H, br s).

- 15 [0302] HPLC (Method B): retention time 8.62 min (97.09%). δ_H (CDCl₃)

Experiment 13.11**Preparation and Analysis of Compound 45**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl)acetamide

- 20 [0303] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 2-fluorophenylacetic acid (18 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine
25 and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (15 mg, 32%). Rf 0.52 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%)=390 (M+H ⁸¹Br, 100), 388 (M+H ⁷⁹Br, 100).

- 30 ¹H-NMR (CDCl₃): δ = 3.79 (2H, s), 3.83 (3H, s), 7.11-7.23 (3H, m), 7.30-7.55 (6H, m), 7.61-7.64 (1H, m).

- [0304] HPLC (Method B): retention time 7.28 min (100%).

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Experiment 13.12**Preparation and Analysis of Compound 46**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide

[0305] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 4-nitrophenylacetic acid (22 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-toluene, 1:1), giving the title compound (9 mg, 18%). Rf 0.19 (ethyl acetate-toluene, 1:1).

MS (AP+): m/z (%) = 417 (M+H ⁸¹Br, 100), 415 (M+H ⁷⁹Br, 100).

¹H-NMR (CDCl₃): δ = 3.83 (3H, s), 3.87 (2H, s), 7.18-7.23 (1H, m), 7.42-7.65 (7H, m), 8.22-8.30 (2H, m).

[0306] HPLC (Method B): retention time 7.22 min (94.30%).

Experiment 13.13**Preparation and Analysis of Compound 47**

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl)acetamide

[0307] A mixture of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (30 mg, 0.12 mmol), 2-methoxyphenylacetic acid (20 mg, 0.12 mmol), 1-hydroxybenzotriazole hydrate (16 mg, 0.12 mmol) and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (46 mg, 0.12 mmol) were dissolved in chloroform (1.5 ml). N,N-Diisopropylethylamine (0.02 ml, 0.13 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured into brine and the organic layer washed with further brine, dried over magnesium sulphate and then concentrated in vacuo. The crude product was purified by column chromatography (chloroform-methanol, 99:1), giving the title compound (18 mg, 38%) as a colourless solid. Rf 0.65 (chloroform-methanol, 98:2).

MS (AP-): m/z (%) = 400 (M-H ⁸¹Br, 90), 398 (M-H ⁷⁹Br, 100).

¹H-NMR (CDCl₃) δ = 3.76 (2H, s), 3.83 (3H, s), 3.98 (3H, s), 6.97-7.06 (2H, m), 7.11-7.16 (1H, m), 7.31-7.50 (4H, m), 7.53 (1H, s), 7.57-7.60 (1H, m), 7.91 (1H, br s).

[0308] HPLC (Method B): retention time 7.16 min (100%).

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[0309] One or the other (as indicated) of the two following synthetic protocols was used to generate each of the compounds below:

Protocol A:

5 [0310] To an isocyanate (1 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (1 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred for 16 hours and concentrated. Chromatography on flash silica (20%-80% EtOAc/hexane) followed by recrystallisation gave the pure urea.

Protocol B:

10 [0311] To a stirred solution of triphosgene (0.33 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of 3-(3-aminophenyl)-4-bromo-2-methylpyrazole (1 mmol) and triethylamine (2 mmol) in CH_2Cl_2 (4 mL). After 1 hour, an aniline was added (1 mmol). The reaction mixture was stirred for 16 hours and concentrated. Chromatography on flash silica (20%-80% EtOAc/hexane) followed by recrystallisation gave the pure urea. :

15

Experiment 13.14

Preparation and Analysis of Compound 11

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino)carboxamide

20 [0312] (Protocol A) – 4-(methylthio)phenyl isocyanate;
colorless solid (EtOAc/hexane).
MS (ES⁺): m/z (%) = 419 (M+H ⁸¹Br, 100), 417 (M+H ⁷⁹Br, 94).
¹H-NMR (MeOH d₄): δ = 2.42 (3H, s, SCH₃), 3.81 (3H, s, NCH₃), 7.06 (1H, m, ArH), 7.22 (2H, m, ArH), 7.37 (2H, m, ArH), 7.42-7.61 (4H, m, ArH).

[0313] HPLC: retention time 3.35 min (Method A).

25

Experiment 13.15

Preparation and Analysis of Compound 8

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino)carboxamide

30 [0314] (Protocol A) – 4-chlorophenyl isocyanate;
colorless solid (EtOAc/hexane).

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MS (ES⁺): m/z (%) = 409 (M+H ⁸¹Br ³⁷Cl, 19), 407 (M+H ⁷⁹Br ³⁷Cl (⁸¹Br ³⁵Cl), 100), 405 (M+H ⁷⁹Br ³⁵Cl, 81).

¹H-NMR (MeOH d₄): δ = 3.81 (3H, s, CH₃), 7.07 (1H, m, ArH), 7.23 (2H, m, ArH), 7.36-7.60 (6H, m, ArH).

5 [0315] HPLC: retention time 3.42 min (Method A).

Experiment 13.16

Preparation and Analysis of Compound 9

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl)carboxamide

- 10 [0316] (Protocol A) – 4-fluorophenyl isocyanate;
colorless solid (EtOAc/hexane).
MS (ES⁺): m/z (%) = 391 (M+H ⁸¹Br, 96), 389 (M+H ⁷⁹Br, 100).
¹H-NMR (MeOH d₄): δ = 3.81 (3H, s, CH₃), 6.93-7.11 (3H, m, ArH), 7.37-7.61 (6H, m, ArH).
- 15 [0317] HPLC: retention time 3.11 min.

Experiment 13.17

Preparation and Analysis of Compound 12

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide

- 20 [0318] (Protocol A) - 2-(trifluoromethoxy)phenyl isocyanate;
colorless solid (EtOAc/hexane).
MS (ES⁺): m/z (%) = 457 (M+H ⁸¹Br, 100), 455 (M+H ⁷⁹Br, 95).
¹H-NMR (DMSO d₆): δ = 3.79 (3H, s, CH₃), 7.06-7.18 (2H, m, ArH), 7.38-7.49 (2H, m, ArH), 7.51-7.62 (2H, m, ArH), 7.65 (1H, m, ArH), 7.71 (1H, s, ArH), 8.24 (1H, dd, J=1.1, 8.2, ArH), 8.56 (1H, s, NH), 9.49 (1H, s, NH).
- 25

[0319] HPLC: retention time 3.40 min.

Experiment 13.18

Preparation and Analysis of Compound 13

- 30 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl)carboxamide

[0320] (Protocol A) - 2-nitrophenyl isocyanate;

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yellow solid (EtOAc/hexane).

MS (ES⁺): m/z (%) = 418 (M+H ⁸¹Br, 98), 416 (M+H ⁷⁹Br, 100).

¹H-NMR (DMSO *d*₆): δ = 3.79 (3H, s, NCH₃), 7.14 (1H, m, ArH), 7.24 (1H, m, ArH), 7.50 (1H, t, J=7.7, ArH), 7.60 (2H, m, ArH), 7.67 (1H, s, ArH), 7.71 (1H, s, ArH), 8.10 (1H, m, ArH), 8.29 (1H, m, ArH), 9.65 (1H, s, NH), 10.09 (1H, s, NH).

[0321] HPLC: retention time 3.10 min (Method A).

Experiment 13.19

Preparation and Analysis of Compound 14

10 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl)carboxamide

[0322] (Protocol A) – 4-methoxyphenyl isocyanate;
colorless solid (EtOAc/hexane).

MS (ES⁺): m/z (%) = 403 (M+H ⁸¹Br, 100), 401 (M+H ⁷⁹Br, 96).

15 ¹H-NMR (DMSO *d*₆): δ = 3.71 (3H, s, OCH₃), 3.79 (3H, s, NCH₃), 6.87 (2H, d, J=8.9, ArH), 7.06 (1H, d, J=7.5, ArH), 7.39 (2H, d, J=8.9, ArH), 7.45-7.61 (3H, m, ArH), 7.65 (1H, s, ArH), 8.52 (1H, s, NH), 8.84 (1H, s, NH).

[0323] HPLC: retention time 3.08 min.

Experiment 13.20

20 Preparation and Analysis of Compound 15

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl)carboxamide

[0324] (Protocol A) – *o*-tolyl isocyanate;
colorless solid (EtOAc/hexane).

MS (ES⁺): m/z (%) = 387 (M+H ⁸¹Br, 94), 385 (M+H ⁷⁹Br, 100).

25 ¹H-NMR (MeOH *d*₄): δ = 2.29 (3H, s, CH₃), 3.81 (3H, s, NCH₃), 7.03 (1H, dt, J=1.1, 7.5, ArH), 7.09 (1H, dt, J=1.1, 7.5, ArH), 7.13-7.22 (2H, m, ArH), 7.45 (1H, t, J=7.9, ArH), 7.49-7.57 (2H, m, ArH), 7.60-7.68 (2H, m, ArH).

[0325] HPLC: retention time 2.96 min.

Experiment 13.21**Preparation and Analysis of Compound 16**

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl)phenyl)carboxamide

[0326] (Protocol A) – 4-(trifluoromethyl)phenyl isocyanate;

5 colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 441 (M+H ^{81}Br , 94), 439 (M+H ^{79}Br , 100).

$^1\text{H-NMR}$ (MeOH d_4): δ = 3.82 (3H, s, CH_3), 7.04-7.16 (3H, m, ArH), 7.20-7.47 (6H, m, ArH).

[0327] HPLC: retention time 3.56 min. :

10

Experiment 13.22**Preparation and Analysis of Compound 17**

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl)carboxamide

[0328] (Protocol A) – 3-chlorophenyl isocyanate;

15 colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 409 (M+H ^{81}Br ^{37}Cl , 26), 407 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 405 (M+H ^{79}Br ^{35}Cl , 70).

$^1\text{H-NMR}$ (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.04 (1H, m, ArH), 7.10 (1H, m, ArH), 7.28 (2H, m, ArH), 7.47 (1H, t, $J=7.8$, ArH), 7.55 (1H, m, ArH), 7.63 (1H, m, ArH), 7.68 (1H, s, ArH), 7.73 (1H, m, ArH), 9.04 (2H, s, NH).

20

[0329] HPLC: retention time 3.20 min (Method A).

Experiment 13.23**Preparation and Analysis of Compound 18**

25 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl)carboxamide

[0330] (Protocol A) – 2-chlorophenyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 409 (M+H ^{81}Br ^{37}Cl , 24), 407 (M+H ^{79}Br ^{37}Cl (^{81}Br ^{35}Cl), 100), 405 (M+H ^{79}Br ^{35}Cl , 72).

30

$^1\text{H-NMR}$ (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.03 (1H, m, ArH), 7.11 (1H, m, ArH), 7.28 (1H, m, ArH), 7.35-7.53 (3H, m, ArH), 7.55 (1H, s, ArH), 7.62 (1H, m, ArH), 8.11 (1H, m, ArH).

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[0331] HPLC: retention time 3.13 min.

Experiment 13.24

Preparation and Analysis of Compound 19

5 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)phenyl)carboxamide

[0332] (Protocol A) – 4-isopropylphenyl isocyanate;

colorless solid (THF/hexane).

MS (ES⁺): m/z (%) = 415 (M+H ⁸¹Br, 100), 413 (M+H ⁷⁹Br, 92).

10 ¹H-NMR (MeOH d₄): δ = 1.23 (6H, d, J=6.8, 2xCH₃), 2.86 (1H, septet, J=6.8, CH),
3.82 (3H, s, NCH₃), 7.09 (1H, m, ArH), 7.16 (2H, d, J=7.6, ArH), 7.31 (2H, d, J=7.6, ArH),
7.42-7.51 (2H, m, ArH), 7.54 (1H, s, ArH), 7.59 (1H, m, ArH).

[0333] HPLC: retention time 3.66 min.

Experiment 13.25

15 Preparation and Analysis of Compound 20

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl)carboxamide

[0334] (Protocol A) – 3-methoxyphenyl isocyanate;

colorless solid (EtOAc/hexane).

MS (ES⁺): m/z (%) = 403 (M+H ⁸¹Br, 100), 401 (M+H ⁷⁹Br, 96).

20 ¹H-NMR (MeOH d₄): δ = 3.73 (3H, s, OCH₃), 3.81 (3H, s, NCH₃), 6.59 (1H, m, ArH), 6.91 (1H, m, ArH), 7.08 (1H, m, ArH), 7.14 (2H, m, ArH), 7.39-7.61 (4H, m, ArH).

[0335] HPLC: retention time 2.90 min.

Experiment 13.26

25 Preparation and Analysis of Compound 21

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl)carboxamide

[0336] (Protocol A) – *m*-tolyl isocyanate; :

colorless solid (EtOAc/hexane).

MS (ES⁺): m/z (%) = 387 (M+H ⁸¹Br, 100), 385 (M+H ⁷⁹Br, 96).

30 ¹H-NMR (DMSO d₆): δ = 2.26 (3H, s, CH₃), 3.76 (3H, s, NCH₃), 6.79 (1H, m, ArH),
7.06-7.22 (3H, m, ArH), 7.29 (1H, m, ArH), 7.43-7.62 (3H, m, ArH), 7.68 (1H, s, ArH), 8.65
(1H, s, NH), 8.89 (1H, s, NH).

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[0337] HPLC: retention time 3.05 min (Method A).

Experiment 13.27**Preparation and Analysis of Compound 22**

5 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-(trifluoromethoxy)phenyl)-carboxamide

[0338] (Protocol B) – *N*-methyl-4-(trifluoromethoxy)aniline;
pale yellow solid (EtOAc/hexane).

MS (ES⁺): *m/z* (%) = 471 (M+H ⁸¹Br, 88), 469 (M+H ⁷⁹Br, 100).

10 ¹H-NMR (MeOH d₄): δ = 3.35 (3H, s, NCH₃), 3.81 (3H, s, NCH₃), 7.09 (1H, m, ArH), 7.25-7.51 (8H, m, ArH).

[0339] HPLC: retention time 3.56 min (Method A).

Experiment 13.28

15 **Preparation and Analysis of Compound 23**

N-(4-(*tert*-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide
(Protocol B) – 4-*tert*-butylaniline;

[0340] colorless solid (EtOAc/hexane).

MS (ES⁺): *m/z* (%) = 429 (M+H ⁸¹Br, 98), 427 (M+H ⁷⁹Br, 100).

20 ¹H-NMR (DMSO d₆): δ = 1.27 (9H, s, 3xCH₃), 3.79 (3H, s, NCH₃), 7.07 (1H, d, J=7.5, ArH), 7.29 (2H, d, J=8.7, ArH), 7.37 (2H, d, J=8.7, ArH), 7.45 (1H, t, J=7.5, ArH), 7.51-7.60 (2H, m, ArH), 7.66 (1H, s, ArH), 8.65 (1H, s, NH), 8.83 (1H, s, NH).

[0341] HPLC: retention time 3.77 min.

25 **Experiment 13.29**

Preparation and Analysis of Compound 24

N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)carboxamide
(Protocol B) – *N,N*-dimethyl-*p*-phenylenediamine;

[0342] colorless solid (EtOAc/hexane).

30 MS (ES⁺): *m/z* (%) = 416 (M+H ⁸¹Br, 96), 414 (M+H ⁷⁹Br, 100).

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¹H-NMR (DMSO d₆): δ = 2.86 (6H, s, NCH₃), 3.80 (3H, s, NCH₃), 6.80 (2H, m, ArH), 7.09 (1H, d, J=7.7, ArH), 7.28 (2H, m, ArH), 7.42 (1H, t, J=7.8, ArH), 7.52 (1H, m, ArH), 7.59 (1H, s, ArH), 7.67 (1H, s, ArH), 8.45 (1H, s, NH), 8.75 (1H, s, NH).

[0343] HPLC: retention time 2.07 min (Method A).

5

Experiment 13.30

Preparation and Analysis of Compound 25

N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)
carboxamide (Protocol B) – 3,5-dichloro-4-methylphenylamine;

10 [0344] colorless solid (EtOAc/hexane).

MS (ES⁺): *m/z* (%) = 457 (M+H, 35), 455 (M+H, 100), 453 (M+H, 65).

¹H-NMR (DMSO d₆): δ = 2.32 (3H, s, CH₃), 3.79 (3H, s, NCH₃), 7.11 (1H, d, J=7.4, ArH), 7.46 (1H, t, J=7.8, ArH), 7.50-7.64 (4H, m, ArH), 7.68 (1H, s, ArH), 9.02 (1H, s, NH), 9.09 (1H, s, NH).

15 [0345] HPLC: retention time 3.66 min.

Experiment 13.31

Preparation and Analysis of Compound 26

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethylthio)phenyl)
carboxamide (Protocol B) – 4-(trifluoromethylthio)aniline;

20

[0346] colorless solid (EtOAc/hexane).

MS (ES⁺): *m/z* (%) = 473 (M+H ⁸¹Br, 100), 471 (M+H ⁷⁹Br, 94).

¹H-NMR (DMSO d₆): δ = 3.81 (3H, s, NCH₃), 7.11 (1H, d, J=7.5, ArH), 7.47 (1H, t, J=7.9, ArH), 7.51-7.63 (6H, m, ArH), 7.66 (1H, s, ArH), 9.03 (1H, s, NH), 9.16 (1H, s, NH).

25 HPLC: retention time 3.76 min.

Experiment 13.32

Preparation and Analysis of Compound 31

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl)carboxamide

30 [0347] (Protocol B) – cyclohexylamine; :

colorless solid, m.p. 155.5-156.3°C (EtOAc/hexane).

MS (ES⁺): *m/z* (%) = 379 (M+H ⁸¹Br, 93), 377 (M+H ⁷⁹Br, 100).

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¹H-NMR (DMSO d₆): δ = 1.07-1.34 (5H, m, 5xCH), 1.52 (1H, m, CH), 1.63 (2H, m, 2xCH), 1.76 (2H, m, 2xCH), 3.48 (1H, m, NCH), 3.74 (3H, s, CH₃), 6.15 (1H, d, J=7.8, ArH), 6.98 (1H, d, J=7.5, ArH), 7.32-7.43 (2H, m, ArH), 7.51 (1H, m, NH), 7.62 (1H, s, ArH), 8.50 (1H, s, NH).

- 5 [0348] HPLC: retention time 3.16 min (Method A). :
 TLC: retention factor 0.35 (50% EtOAc/hexane).

Experiment 13.33

Preparation and Analysis of Compound 32

- 10 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl)carboxamide

- [0349] (Protocol B) – benzylamine;
 colorless solid, m.p. 144.5-146.2°C (EtOAc/hexane).
 IR: ν_{\max} = 1622, 1565, 1467, 1374, 1239, 973, 802, 752, 695 cm⁻¹.
 MS (ES⁺): *m/z* (%) = 387 (M+H ⁸¹Br, 89), 385 (M+H ⁷⁹Br, 100).
15 ¹H-NMR (CD₃OD): δ = 3.81 (3H, s, CH₃), 4.40 (2H, s, CH₂), 7.05 (1H, m, ArH),
 7.19-7.51 (9H, m, ArH).

- [0350] HPLC: retention time 3.06 min (Method A).

Experiment 13.34

- 20 Preparation and Analysis of Compound 27

 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl)carboxamide

- [0351] (Protocol A) – 2-fluorophenyl isocyanate;
 colorless solid (DCM/hexane).
 MS (ES⁺): *m/z* (%) = 391 (M+H ⁸¹Br, 100), 389 (M+H ⁷⁹Br, 90).
25 ¹H-NMR (MeOH d₄): δ = 3.79 (3H, s, NCH₃), 7.00-7.11 (4H, m, ArH), 7.40-7.56
 (3H, m, ArH), 7.61 (1H, m, ArH), 8.09 (1H, m, ArH).

- [0352] HPLC: retention time 3.01 min.

Experiment 13.35

- 30 Preparation and Analysis of Compound 28

 2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino)benzamide

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[0353] (Protocol B) – 2-aminobenzamide;

colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 399 (M+H - 17 ^{81}Br , 100), 397 (M+H - 17 ^{79}Br , 94).

5 $^1\text{H-NMR}$ (DMSO d_6): δ = 3.79 (3H, s, NCH_3), 6.93-7.10 (2H, m, ArH), 7.45 (2H, t, $J=7.8$, ArH), 7.59-7.72 (5H, m, ArH), 8.22 (2H, m), 9.92 (1H, s, NH), 10.69 (1H, s, NH).

[0354] HPLC: retention time 2.88 min.

Experiment 13.36

Preparation and Analysis of Compound 29

10 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl)carboxamide

[0355] (Protocol B) – 4-aminobenzonitrile;

colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 398 (M+H ^{81}Br , 100), 396 (M+H ^{79}Br , 96).

15 $^1\text{H-NMR}$ (MeOH d_4): δ = 3.81 (3H, s, NCH_3), 7.12 (1H, m, ArH), 7.46-7.57 (3H, m, ArH), 7.62-7.69 (5H, m, ArH).

[0356] HPLC: retention time 3.12 min.

Experiment 13.37

Preparation and Analysis of Compound 30

20 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl)carboxamide

[0357] (Protocol B) – 2-aminobenzonitrile;

colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 398 (M+H ^{81}Br , 95), 396 (M+H ^{79}Br , 100).

25 $^1\text{H-NMR}$ (CDCl_3): δ = 3.79 (3H, s, CH_3), 7.13-7.28 (2H, m, ArH), 7.49 (1H, t, $J=7.8$, ArH), 7.57 (1H, m, ArH), 7.62 (1H, m, ArH), 7.65-7.71 (2H, m, ArH), 7.78 (1H, m, ArH), 8.07 (1H, d, $J=8.6$, ArH), 8.83 (1H, s, NH), 9.62 (1H, s, NH).

[0358] HPLC: retention time 3.05 min (Method A).

Experiment 13.38

30 Preparation and Analysis of Compound 33

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenylmethyl)carboxamide

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[0359] (Protocol B) – 4-fluorobenzylamine;

colorless solid, m.p. 185.5-186.6°C (EtOAc/hexane).

MS (ES⁺): m/z (%) = 405 (M+H ⁸¹Br, 97), 403 (M+H ⁷⁹Br, 100).

5 ¹H-NMR (DMSO d₆): δ = 3.75 (3H, s, CH₃), 4.28 (2H, d, J=6.0, CH₂), 6.73 (1H, t, J=5.9, NH), 7.01 (1H, d, J=7.5, ArH), 7.10-7.18 (2H, m, ArH), 7.27-7.41 (4H, m, ArH), 7.56 (1H, s, ArH), 7.62 (1H, s, ArH), 8.82 (1H, s, NH).

[0360] HPLC: retention time 3.10 min (Method A).

[0361] TLC: retention factor 0.25 (50% EtOAc/hexane).

10 Experiment 13.39

Preparation and Analysis of Compound 34

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-dimethoxyphenylmethyl)carboxamide

[0362] (Protocol B) – 3,4-dimethoxybenzylamine:

15 colorless solid, m.p. 174.9-175.5°C (EtOAc/hexane).

MS (CI⁺): m/z (%) = 447 (M+H ⁸¹Br, 100), 445 (M+H ⁷⁹Br, 92).

¹H-NMR (DMSO d₆): δ = 3.71 (3H, s, CH₃), 3.73 (3H, s, CH₃), 3.76 (3H, s, CH₃), 4.22 (2H, d, J=5.8, CH₂), 6.62 (1H, t, J=5.7, NH), 6.80 (1H, m, ArH), 6.89 (2H, m, ArH), 6.98 (1H, m, ArH), 7.36-7.51 (3H, m, ArH), 7.63 (1H, s, ArH), 8.76 (1H, s, NH).

20 [0363] HPLC: retention time 2.86 min (Method A).

[0364] TLC: retention factor 0.20 (50% EtOAc/hexane).

Experiment 13.40

Preparation and Analysis of Compound 35

25 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-trimethoxyphenylmethyl)carboxamide

[0365] (Protocol B) – 3,4,5-trimethoxybenzylamine;

colorless solid (EtOAc/hexane).

MS (CI⁺): m/z (%) = 477 (M+H ⁸¹Br, 100), 475 (M+H ⁷⁹Br, 95).

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¹H-NMR (DMSO d₆): δ = 3.63 (3H, s, OCH₃), 3.75 (9H, s, 3xCH₃), 4.21 (1H, d, J=5.9, CH₂), 6.61 (2H, s, ArH), 6.65 (1H, t, J=5.9, NH), 6.99 (1H, m, ArH), 7.40 (1H, t, J=7.7, ArH), 7.45 (1H, m, ArH), 7.56 (1H, m, ArH), 7.64 (1H, s, ArH), 8.77 (1H, s, NH).

[0366] HPLC: retention time 5.91 min (Method B).

5 [0367] TLC: retention factor 0.50 (50% EtOAc/hexane).

Experiment 13.41

Preparation and Analysis of Compound 36

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl)amino)carboxamide

10 [0368] (Protocol B) – 2-methylbenzylamine;
colorless solid (EtOAc/hexane).

MS (CI⁺): *m/z* (%) = 401 (M+H ⁸¹Br, 96), 399 (M+H ⁷⁹Br, 100).

¹H-NMR (DMSO d₆): δ = 2.28 (3H, s, CH₃), 3.76 (3H, s, NCH₃), 4.28 (1H, d, J=5.8, CH₂), 6.60 (1H, t, J=5.8, NH), 7.01 (1H, m, ArH), 7.15 (3H, m, ArH), 7.24 (1H, m, ArH),
15 7.38-7.50 (2H, m, ArH), 7.57 (1H, m, ArH), 7.65 (1H, s, ArH), 8.77 (1H, s, NH).

[0369] HPLC: retention time 2.74 min (Method A).

[0370] TLC: retention factor 0.20 (50% EtOAc/hexane).

Experiment 13.42

20 Preparation and Analysis of Compound 37

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenylmethyl)carboxamide

[0371] (Protocol B) – 4-methoxybenzylamine;
colorless solid (EtOAc/hexane).

MS (CI⁺): *m/z* (%) = 417 (M+H ⁸¹Br, 94), 415 (M+H ⁷⁹Br, 100).

¹H-NMR (DMSO d₆): δ = 3.72 (3H, s, CH₃), 3.77 (3H, s, NCH₃), 4.22 (1H, d, J=5.9, CH₂), 6.62 (1H, t, J=5.9, NH), 6.90 (2H, d, J=8.8, ArH), 7.00 (1H, m, ArH), 7.23 (2H, d, J=8.8, ArH), 7.39 (1H, t, J=7.8, ArH), 7.43 (1H, m, ArH), 7.56 (1H, m, ArH), 7.64 (1H, s, ArH), 8.73 (1H, s, NH).

[0372] HPLC: retention time 6.41 min (Method B).

30 [0373] TLC: retention factor 0.25 (50% EtOAc/hexane).

Experiment 13.43**Preparation and Analysis of Compound 38**

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide

5 [0374] (Protocol B) – 2-(4-methoxyphenyl)ethylamine;
colorless solid (EtOAc/hexane).

MS (ES+): m/z (%) = 431 (M+H ^{81}Br , 95), 429 (M+H ^{79}Br , 100).

$^1\text{H-NMR}$ (DMSO d_6): δ = 2.68 (2H, t, $J=7.1$, CH_2), 3.31 (2H, m, CH_2), 3.71 (3H, s, CH_3), 3.77 (3H, s, CH_3), 6.16 (1H, t, $J=5.8$, NH), 6.87 (2H, d, $J=8.6$, ArH), 6.99 (1H, dt, $J=1.4, 7.3$, ArH), 7.16 (2H, d, $J=8.6$, ArH), 7.33-7.48 (2H, m, ArH), 7.52 (1H, m, ArH), 7.63 (1H, s, ArH), 8.71 (1H, s, NH).

10

[0375] HPLC: retention time 6.62 min (Method B).

15 **EXAMPLE 14**

Experiments 14.1 – 14.19**General Synthetic Strategies, Preparation and Analysis of Compounds**

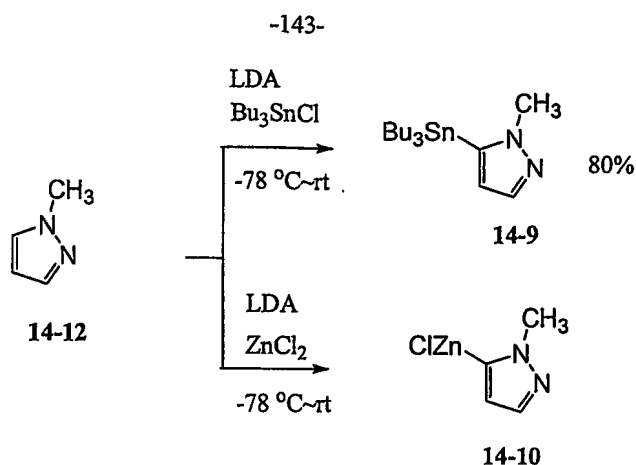
[0376] Compounds of certain embodiments of the invention were prepared according to the procedures below.

20

General Synthetic Strategies

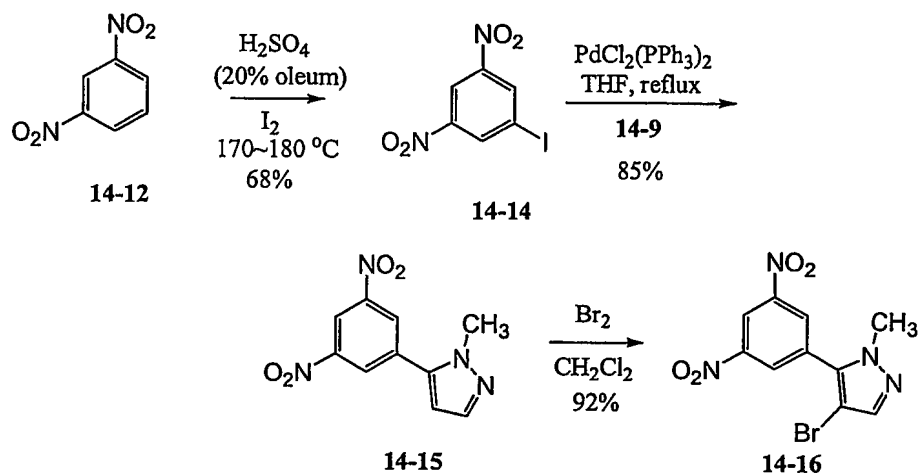
[0377] Tributyltin pyrazole **14-9** was synthesized from pyrazole **14-12** in 80 % chemical yield. Pyrazole **14-12** was directly lithiated with LDA at -78°C followed by quenching with Bu_3SnCl . Tributyltin pyrazole **14-9** is fairly stable on silica gel and can be stored at room temperature without any decomposition for up to one month in the air. Zinc pyraole **14-10** was also formed under lithiation with LDA or $n\text{-BuLi}$ at -78°C followed by quenching with ZnCl_2 in high yields. Zinc pyraole **14-10** was freshly synthesized for coupling reactions (Scheme 14-1).

25



Scheme 14-1

[0378] 1,3-Dinitrobenzene 14-13 was commercially available and iodinated with I₂ and H₂SO₄ (oleum) to afford iodobenzene 14-14 in 68 % yield. Iodobenzene 14-14 was coupled with tributyltin pyrazole 14-9 under 7 % PdCl₂(PPh₃)₂ to afford coupled product 14-15 in 85 % yield which could also be separable by recrystallization in ethanol and synthesize in quantity (i.e., 20g scale). Regiospecific bromination of 14-15 occurred smoothly under Br₂ in dichloromethane at room temperature (Scheme 14-2).



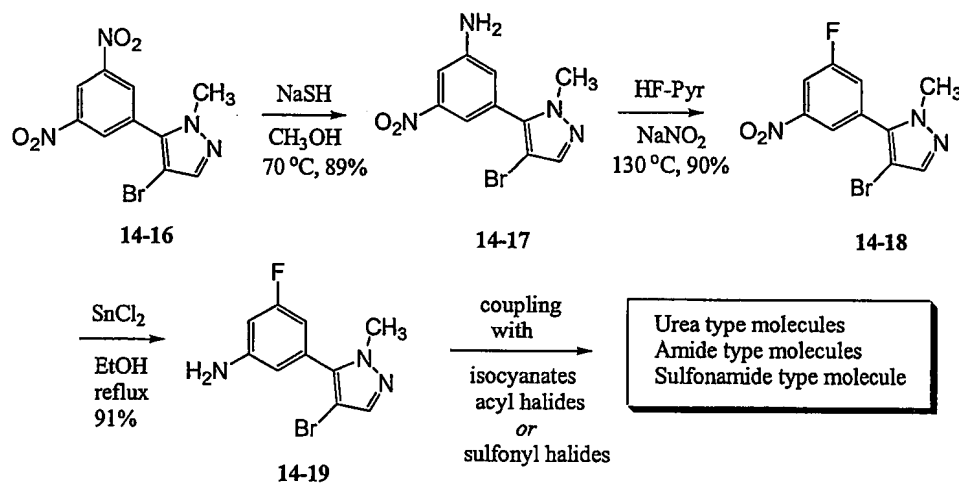
Scheme 14-2

[0379] A number of reagents have been used for selective reduction of nitroaromatic compounds, the most common being alcoholic basic hydrogen sulfide, alcoholic ammonium sulphide, and alcoholic sodium polysulphide. However, the product amines from these reactions are generally obtained in low yields and are often difficult to purify. The hydrosulfide-induced reaction was investigated intensively by Idoux and is superior to the previously reported method. Based on this

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result, dinitro 14-16 was reduced to aniline 14-17 with NaSH in CH₃OH; 2.7 equivalents of NaSH were needed to complete the reaction. Double reduced compound was also detected on the LCMS, but it was less than 5 % (Scheme 14-3).

[0380] Aniline 14-17 was also fluorinated under HF•Pyr and NaNO₂ to furnish 14-18 in 90 % yield. 14-18 could be reduced with SnCl₂ as a usual way to form flouroaniline 14-19 in 91 % yield. The precursor 14-19 was coupled with various isocyanates, acyl halides and sulfonyl halides to form urea, amide and sulfonamide type molecules respectively in good yields (Scheme 14-3).

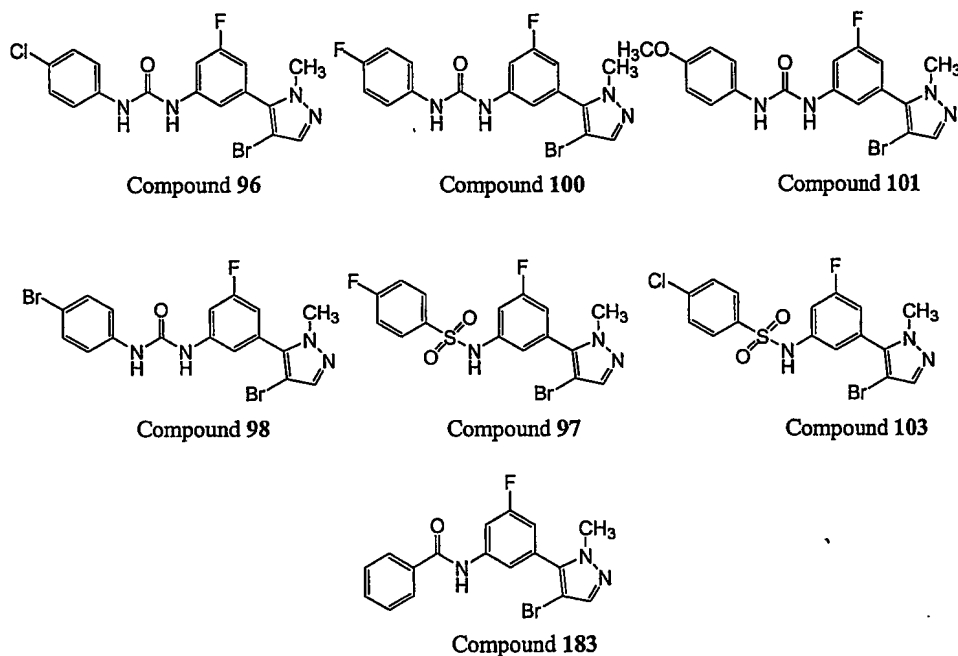


Scheme 14-3

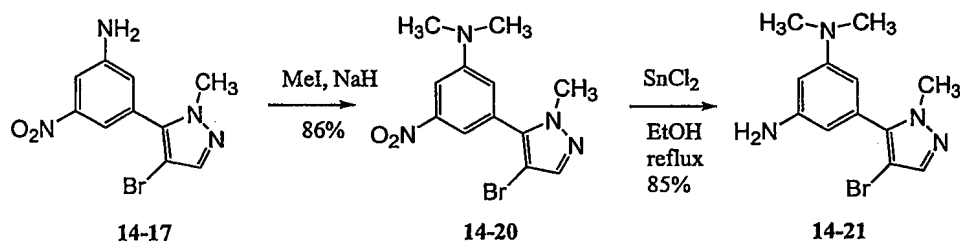
10 [0381] The following contains the list of representative fluorinated compounds synthesized (TABLE 14-1).

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Table 14-1 Compounds of the invention containing a fluoride functionality.



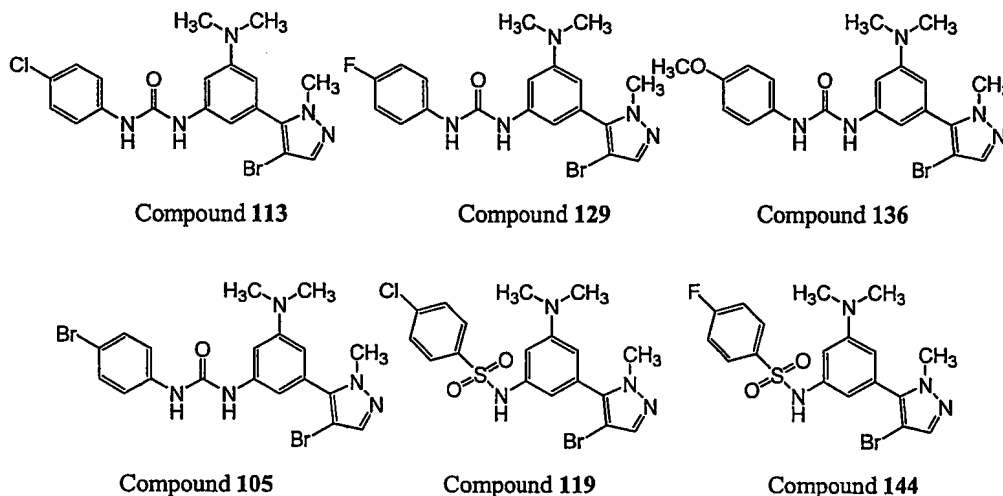
[0382] In addition, as shown in Scheme 14-3, aniline 14-17 was also alkylated with 2 equivalents of CH_3I and NaH at room temperature in 86 % yield. Finally, 14-17 was reduced with $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in EtOH at a reflux condition to furnish the aminomethylated precursor 14-21 in 85 % yield (Scheme 14-4).



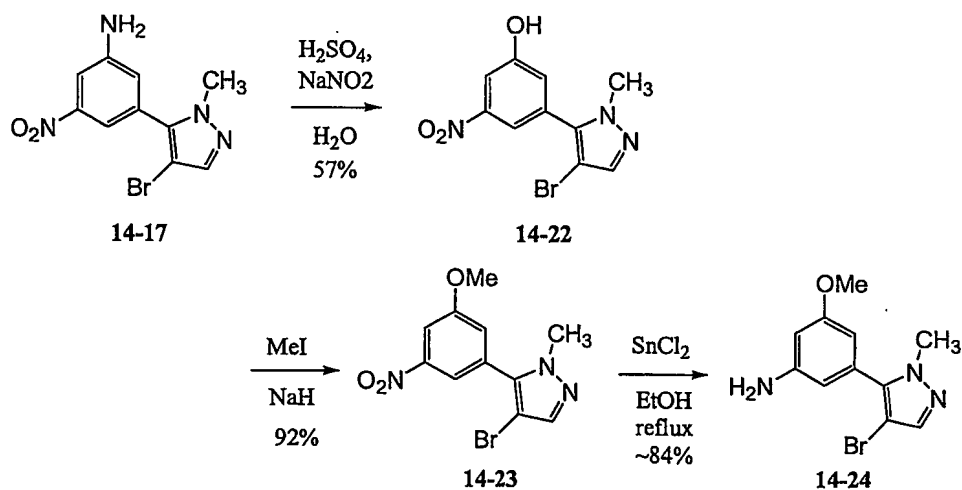
Scheme 14-4

[0383] Aniline 14-21 was coupled with various isocyanates, acyl chlorides and sulfonyl chlorides to form aminodimethylated compound of the invention in high yields (TABLE 14-2).

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Table 14-2 Compounds of the invention containing *N,N*-dimethylamino functionality.

[0384] The amino group on aniline 14-17 was transformed into a hydroxy group under H_2SO_4 and NaNO_2 to give phenol 14-22 in a 57 % yield. Phenol 14-22 was methylated with MeI and NaH in DMF followed by reduction with $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in EtOH providing aniline 14-24 in good yields (Scheme 14-5).

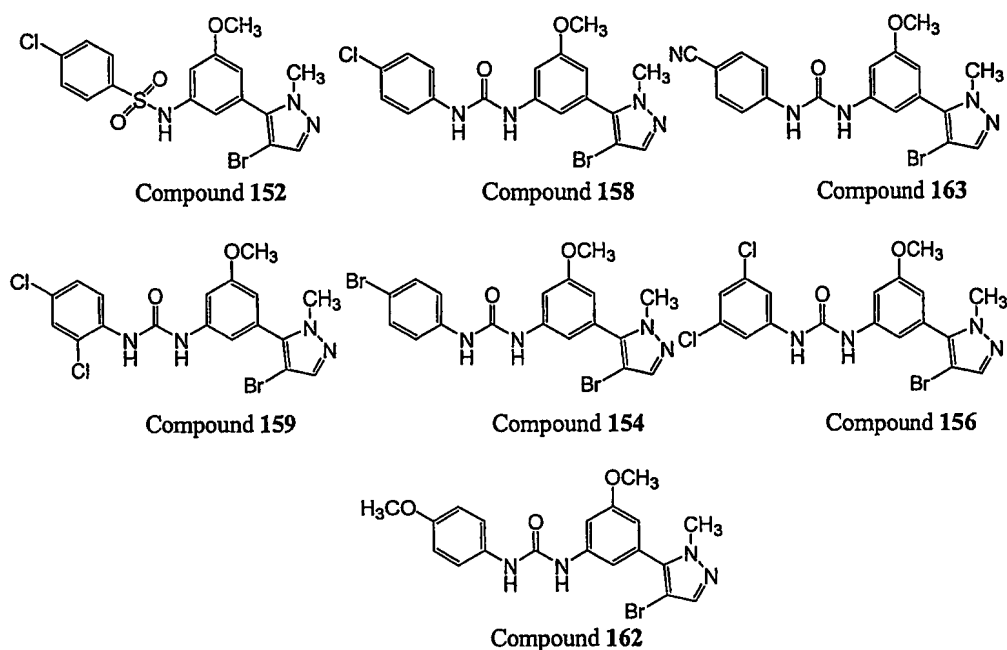


Scheme 14-5

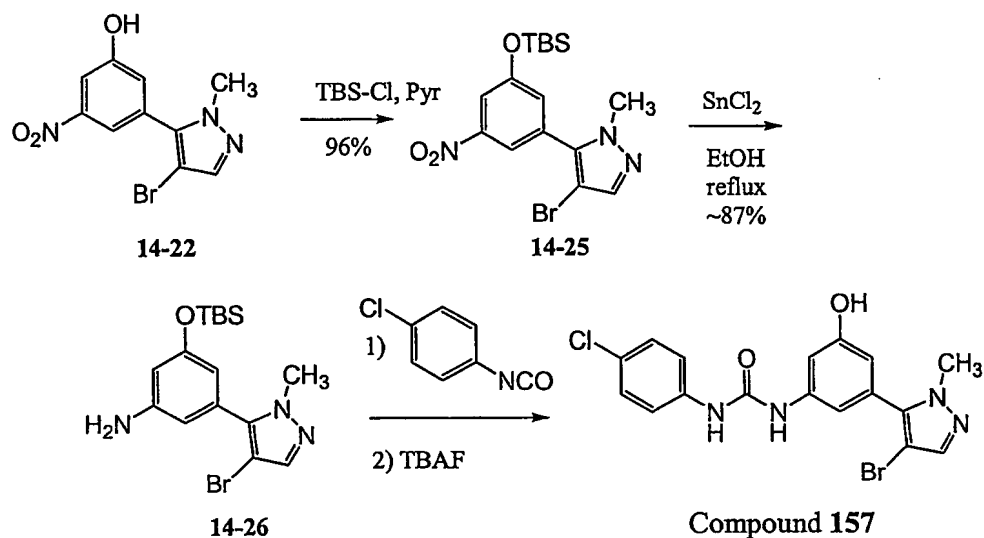
10 [0385] Aniline 14-24 was coupled with various isocyanates, acyl chlorides and sulfonyl chlorides to furnish the compounds of the invention containing a methoxy group (TABLE 14-3).

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Table 14-3 Compounds of the invention containing methoxy functionality.



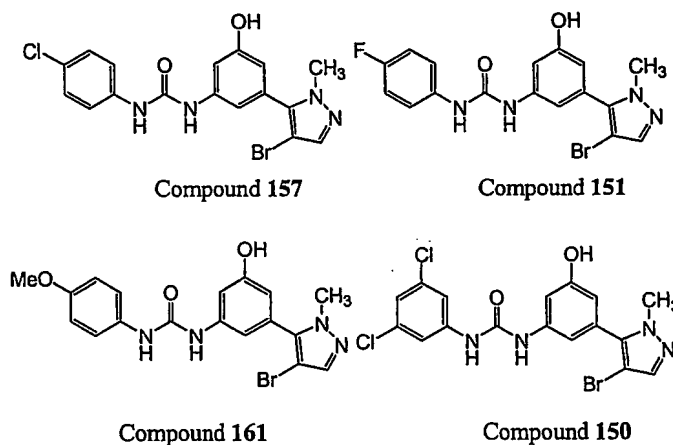
[0386] An introduction of a hydroxy group on the aromatic ring was also attempted. Phenol 14-22 was protected with TBS-Cl in pyridine at room temperature followed by reduction with $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in EtOH to afford silyl ether 14-25 in high yield. After reduction with SnCl_2 , aniline 14-26 was coupled with 4-chlorophenyl isocyanate at room temperature and deprotected with TBAF *in situ* to furnish Compound 157 of the invention in 89 % yield after column chromatography on silica gel (Scheme 14-6).



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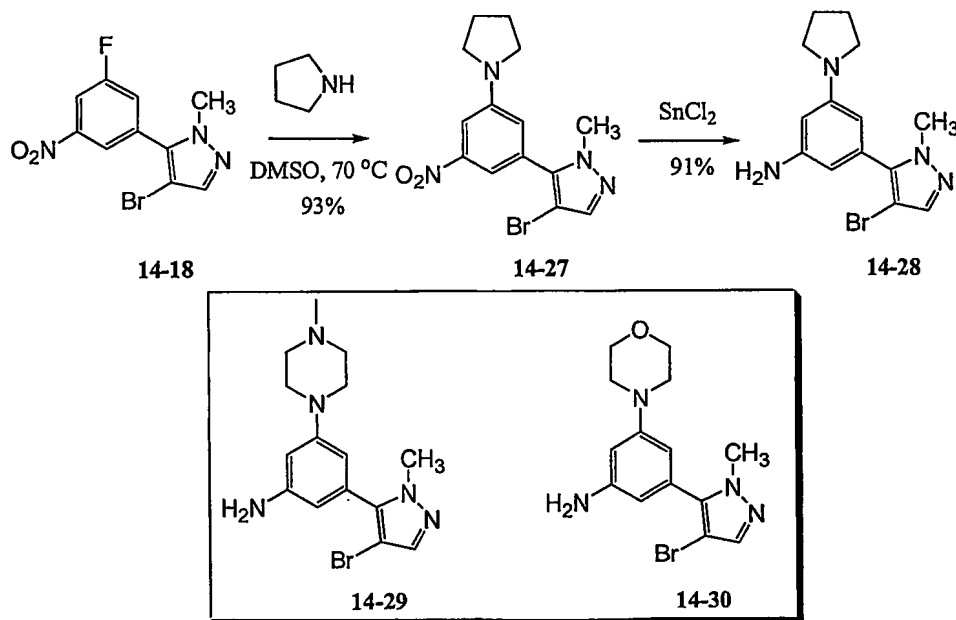
[0387] The list of compounds of the invention containing a hydroxy functionality is shown below (TABLE 14-4).

Table 14-4 Compounds of the invention containing hydroxy functionality



5

[0388] Several attempts for introduction of cycloamines on the aromatic group have been made. The direct substitution reaction of various cyclic amines under mild conditions gave desired products. For these reactions, DMSO is the choice of solvents (Scheme 14-7).



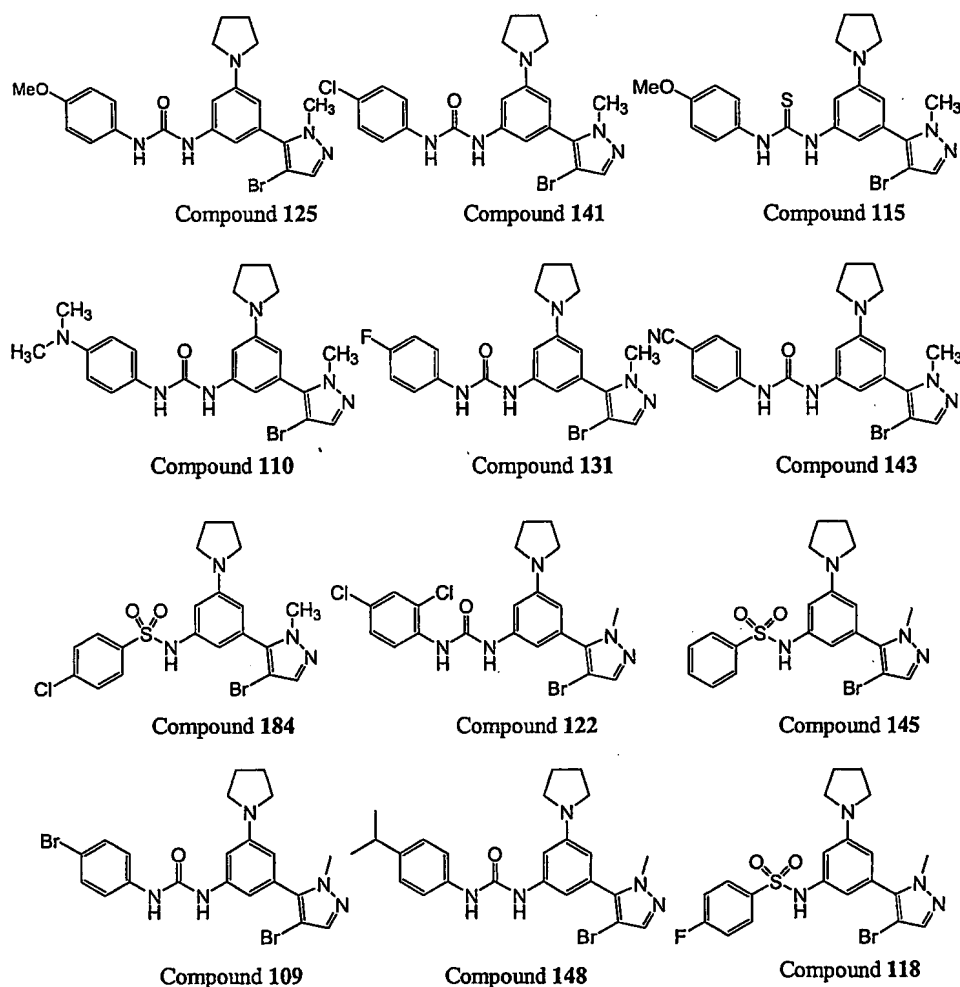
Scheme 14-7

10

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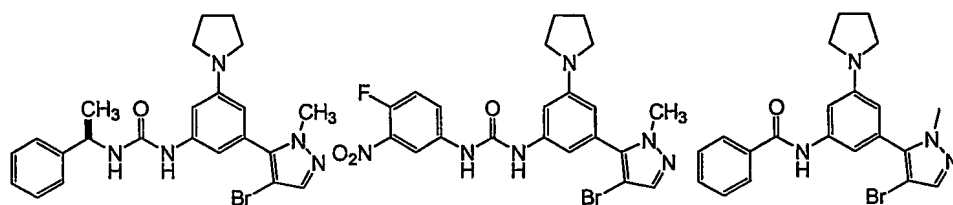
[0389] Fluoro phenyl 14-18 was treated with pyrrolidine in DMSO to afford 14-27 in 93% yield. Subsequently, pyrrolidine 14-27 was reduced with four equivalents of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in EtOH to furnish the precursor 14-28 in 91 % yield. *N*-Methyl piperazine and morpholine were introduced to the aromatic group in the same manner to achieve the precursors 14-29 and 14-30 respectively. With these precursors available, the coupling reactions were completed with various isocyanates, acyl chlorides and sulfonyl chlorides. TABLES 14-5, 14-6 and 14-7 show additional compounds of the invention.

Table 14-5 Compounds of the invention containing pyrrolidine functionality.



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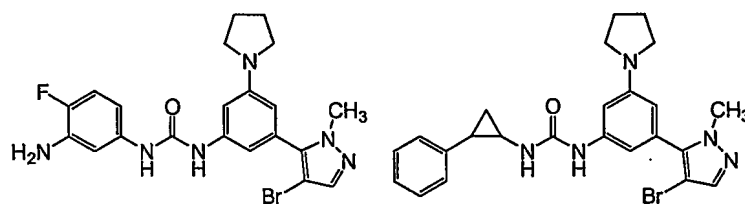
Table 14-5 Continued



Compound 106

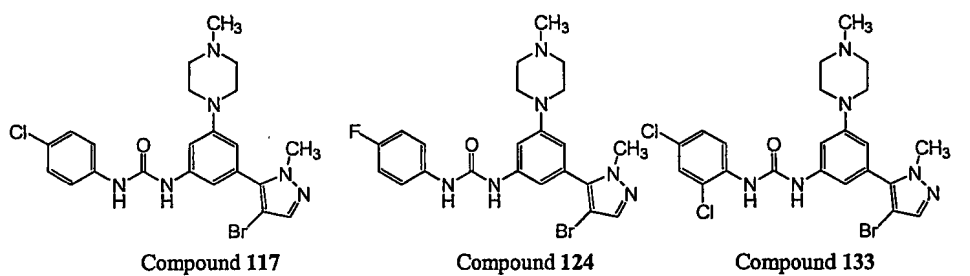
Compound 137

Compound 108



Compound 135

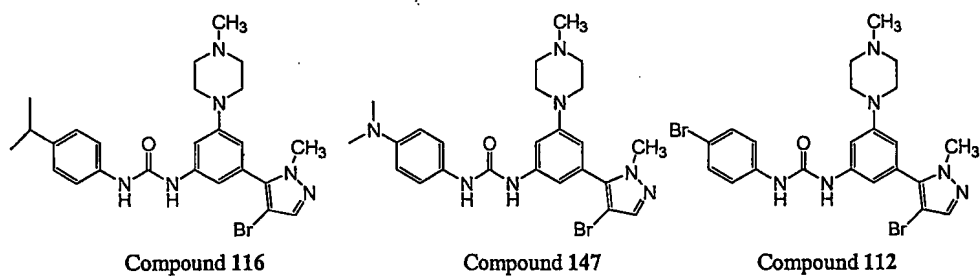
Compound 140

Table 14-6 Compounds of the invention containing *N*-methyl piperazine functionality.

Compound 117

Compound 124

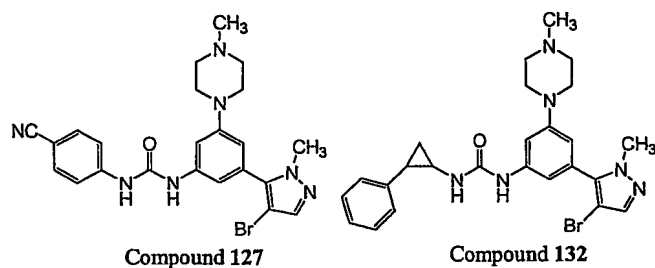
Compound 133



Compound 116

Compound 147

Compound 112

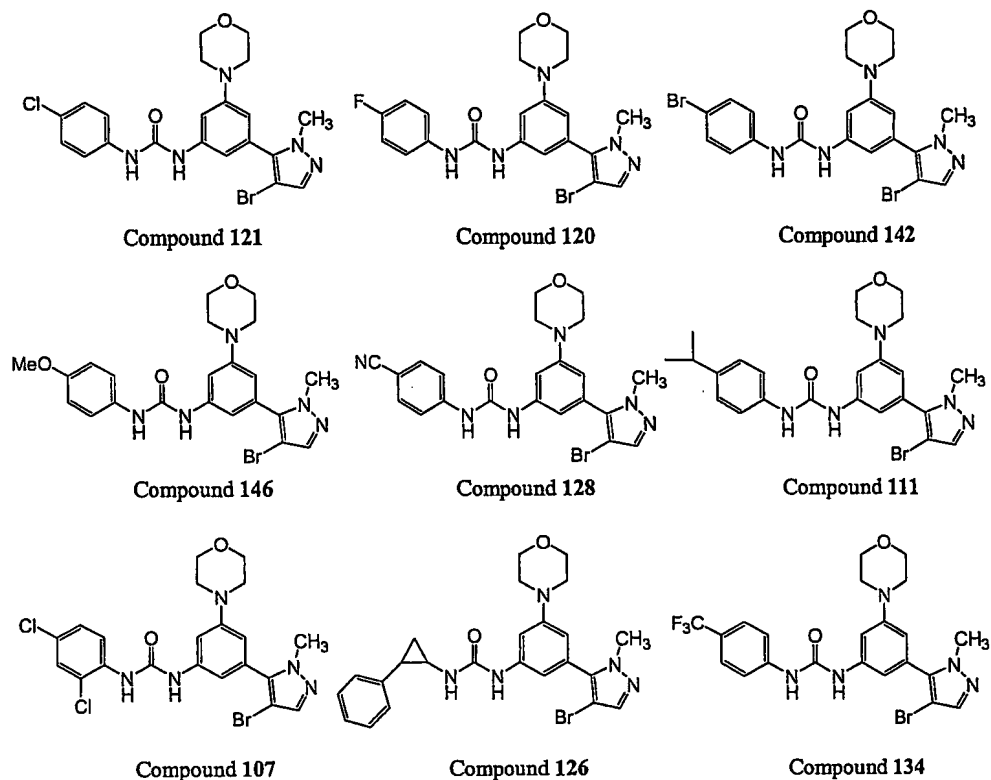


Compound 127

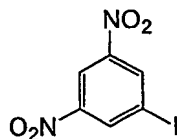
Compound 132

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Table 14-7 Compounds of the invention containing morpholine functionality.

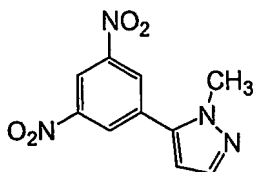
**Experiment 14.1****5 Preparation and Analysis of Compound**

1,3-Dinitro iodobenzene 14-14:



[0390] 1,3-Dinitrobenzene (10 g, 59.5 mmol) and I₂ (7.5 g, 29.5 mmol) were dissolved in 20% oleum (75.9 g) and heated to 170 °C for 45 min. The reaction mixture was maintained at 170~180 °C for 1hr. The temperature was lowered to room temperature. The mixture was poured into crushed ice (500 g) and stirred for 2 hrs. The solid material was filtered and washed with H₂O (500 mL). The solid was dissolved in EtOAc (250 mL) and washed with H₂O (150 mL x 2). The EtOAc was dried over MgSO₄ and concentrated under vacuum to afford to the desired product 14-14 in 62 % yield (10.8 g). R_f = 0.52 (EtOAc/Hex = 1/4).

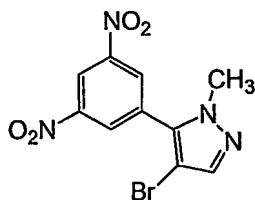
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Experiment 14.2**Preparation and Analysis of Compound****Pyrazole 14-15**

- 5 [0391] Iodobenzen 14-14 (2 g, 6.8 mmol) was dissolved in anhydrous THF (20 mL) and treated with tributyltin pyrazole 14-9 (2.5 g, 6.8 mmol, see Scheme 14-1) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.48 g, 0.68 mmol). The mixture was heated to reflux. After refluxing for 12hrs, the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in EtOAc (50 mL) and washed with H_2O (50 mL x 2). The EtOAc was dried over MgSO_4 and concentrated under vacuum. The crude compound was recrystallized in EtOH (30 mL) to afford the desired coupled product 14-15 (1.41 g, 84 %). $R_f = 0.5$ (EtOAc/Hex = 1/3).
- 10

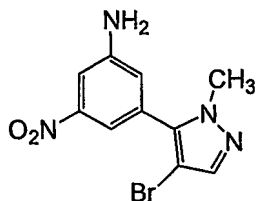
Experiment 14.3**Preparation and Analysis of Compound**

- 15 Bromo pyrazole 14-16



- [0392] To a solution of 14-15 (0.4 g, 1.6 mmol) in dichloromethane (5 mL), was added dropwise Br_2 (91 μL , 1.77 mmol) in dichloromethane (1 mL) for 5 min at 0 °C. After addition of Br_2 , the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H_2O (10 mL) and triturated with EtOH to afford yellowish crystals of the desired product (0.46 g, 92 %) $R_f = 0.72$ (EtOAc/Hex = 1/2).
- 20

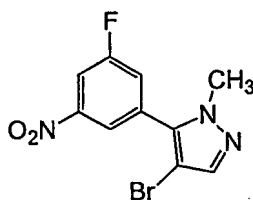
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Experiment 14.4**Preparation and Analysis of Compound****Aniline 14-17**

- 5 [0393] Dinitrophenyl 14-16 (0.6 g, 1.8 mmol) was dissolved in MeOH (40 mL) and toluene (10 mL) and heated to refluxing. NaSH (262 mg, 4.68 mmol) in MeOH (10 mL) was added into the solution for 45 min. The reaction mixture was stirred for 30 min at the same temperature and cooled to room temperature. The reaction mixture was concentrated under vacuum and dissolved in EtOAc (20 mL). The EtOAc was washed with H₂O (20 mL x 2) and dried over MgSO₄. The crude product
- 10 was purified over column chromatography (R_f = 0.51, EtOAc/Hex = 1/1) to afford a yellow solid as the desired product 14-17 (487 mg, 91 %).

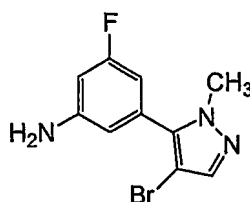
Experiment 14.5**Preparation and Analysis of Compound**

- 15 Fluorophenyl pyrazole 14-18

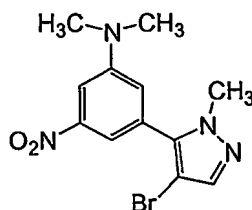


- [0394] Aniline 14-17 (0.3 g, 1.01 mmol) was added into HF•Pyr (2.6 mL) at 0 °C and warmed to room temperature. After stirring for 30 min, the solution was cooled to -30 °C and NaNO₂
- 20 (77 mg, 1.11 mmol) added portionwise for 10 min. The reaction mixture was maintained at -30 °C for 30 min. The mixture was then heated to 145 °C and stirred for 10 min. The reaction mixture was cooled to room temperature and quenched with crushed ice (10 mL). The crude product was extracted with EtOAc (20 mL), dried over MgSO₄ and concentrated under vacuum. The crude material was purified by column chromatograph (EtOAc/Hex = 1/1, R_f = 0.85) to afford a yellow crystal as desired
- 25 product 14-17 (275 mg, 91%).

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Experiment 14.6**Preparation and Analysis of Compound****Fluoro aniline 14-19**

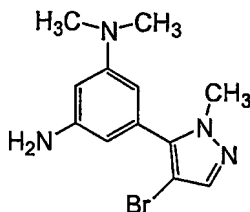
- 5 [0395] A 5 mL round-bottom flask was charged with 100 mg of 14-18 (0.33 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.3 g, 1.33 mmol) and dissolved in EtOH (3 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was under concentrated under vaccum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over MgSO_4 , concentrated under vaccum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of the
- 10 desired product 14-19 (79 mg, 89%).

Experiment 14.7**Preparation and Analysis of Compound****Dimethyl aniline 14-20**

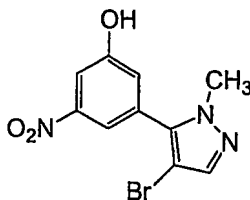
15

- [0396] Aniline 14-17 (1.0 g, 3.36 mmol) was dissolved in DMF (5 mL) in a 10 mL round-bottom flask. The solution was cooled to 0 °C and treated with 60 % NaH (404 mg, 10.08 mmol). The reaction mixture was maintained at the same temperature for 30 min and warmed to room temperature. The mixture was quenched with 100 μL of EtOH and extracted with EtOAc (20 mL).
- 20 The EtOAc was dried over MgSO_4 and concentrated under vaccum. The residue was purified over silica gel (EA/Hex = 1/1, R_f = 0.81) to afford yellow solids as the desired product 14-20 (858 mg, 86%).

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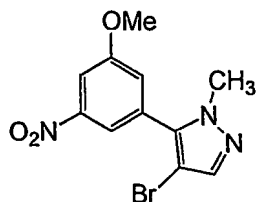
Experiment 14.8**Preparation and Analysis of Compound****Aniline 14-21**

- 5 [0397] A 5 mL round-bottom flask was charged with 103 mg of **14-20** (0.33 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.3 g, 1.33 mmol) and dissolved in EtOH (3 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (20 mL x 2) and H_2O (20 mL). The EtOAc was dried over MgSO_4 , concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal as desired
- 10 product **14-21** (82 mg, 85%).

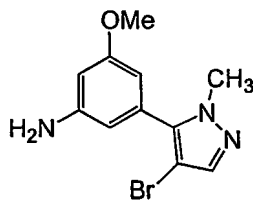
Experiment 14.9**Preparation and Analysis of Compound****Phenol 14-22**

- 15
- [0398] Aniline **14-17** (2 g, 6.73 mmol) was dissolved in H_2SO_4 (5 mL) and H_2O (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 30 min. The solution was treated with NaNO_2 (557 mg, 808 mmol) at -30 °C and stirred for 1 hr. The reaction mixture was heated to 100 °C and stirred for 1 hr. The resulting mixture was cooled to room temperature and quenched with crushed ice (10 g). The mixture was extracted with EtOAc (20 mL x 2). The EtOAc was dried over MgSO_4 and concentrated under vacuum. The residue was purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.52) to afford the white crystals of desired product **14-22** (1.13 g, 57%).
- 20

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Experiment 14.10**Preparation and Analysis of Compound****Anisole 14-23**

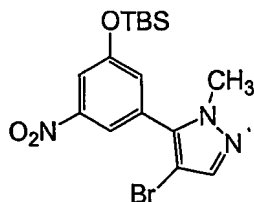
- 5 [0399] To a cooled solution of phenol 14-22 (657 mg, 2.2 mmol) in DMF (5 mL) was treated with 60 % NaH (106 mg, 2.65 mmol). The resulting mixture was stirred at 0 °C and treated with CH₃I (165 μL, 2.65 mmol). The reaction mixture was stirred for 1 hr and warmed to room temperature. The mixture was poured into H₂O (10 mL) and extracted with EtOAc (10 mL x 2). The EtOAc was dried over MgSO₄ and concentrated under vacuum. The residue was purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.75) to afford desired anisole 14-23 (629 mg, 92%).
- 10

Experiment 14.11**Preparation and Analysis of Compound****Aniline 14-24**

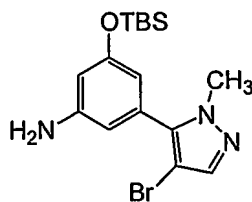
15

- [0400] A 25 mL round-bottom flask was charged with 103 mg of anisole 14-23 (2.08 mmol) and SnCl₂·2H₂O (2.13 g, 8.36 mmol) and dissolved in EtOH (10 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (30 mL x 2) and H₂O (30 mL). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desired product 14-24 (489 mg, 84 %).
- 20

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Experiment 14.12**Preparation and Analysis of Compound****Silyl ether 14-25**

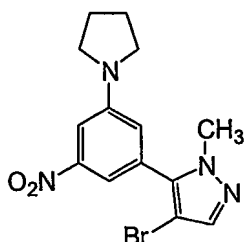
- 5 [0401] To a solution of phenol 14-22 (1g, 3.38 mmol) dissolved in pyridine (3 mL) was added TBS-Cl (611 mg, 4.05 mmol) and the resulting solution was allowed to stir for 10 hrs. The reaction mixture was poured into H₂O (20 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL) dried over MgSO₄ and concentrated under vacuum to afford crude product 14-25 (1.36 g, 96%). The crude product was used for the next step without further
- 10 purification (EtOAc/Hex = 1/1, R_f = 0.89).

Experiment 14.13**Preparation and Analysis of Compound****Aniline 14-26**

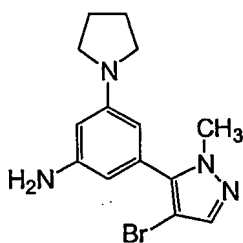
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- [0402] A 25 mL round-bottom flask was charged with 1.0 g of 14-25 (2.4 mmol) and SnCl₂·2H₂O (2.19 g, 9.7 mmol) and dissolved in EtOH (10 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (30 mL x 2) and H₂O (30 mL). The EtOAc was dried over MgSO₄, concentrated under
- 20 vacuum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desired product 14-26 (798 mg, 87 %).

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Experiment 14.14**Preparation and Analysis of Compound****Pyrrolidine 14-27**

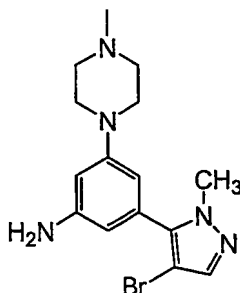
- 5 [0403] Fluorophenyl pyrazole 14-18 (2.6 g, 8.67 mmol) was directly weighed into a 50 mL round-bottom flask and dissolved in DMSO (10 mL). The solution was treated with pyrrolidine (2.2 mL, 26 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H₂O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL), dried over MgSO₄ and concentrated under vacuum. The residue was purified over silica gel to afford the desired
- 10 product 14-27 (2.77 g, 93%).

Experiment 14.15**Preparation and Analysis of Compound****Aniline 14-28**

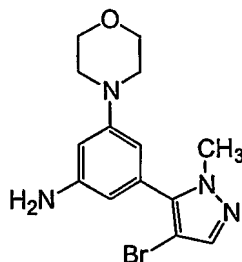
15

- [0404] A 50 mL round-bottom flask was charged with 2.0 of Pyrrolidine 14-27 (5.7 mmol) and SnCl₂·2H₂O (5.8 g, 22.8 mmol) charged dissolved in EtOH (30 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and
- 20 extracted with EtOAc (50 mL x 2) and H₂O (50 mL). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.41) to afford a white crystal of desire product 14-28 (1.66 g, 91 %):.

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Experiment 14.16**Preparation and Analysis of Compound****N-Methylpiperazine 14-29**

- 5 [0405] Fluorophenyl pyrazole 14-18 (2.6 g, 8.67 mmol) was directly weighed into a 50 mL round-bottom flask and dissolved in DMSO (10 mL). The solution was treated with 4-methylpiperazine (1.5 mL, 17.3 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H₂O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was washed with 1.0 N HCl (10 mL), dried over MgSO₄ and concentrated under vacuum. The crude product was used for the
- 10 next step without further purification. A 100 mL round-bottom flask was charged with the crude compound and SnCl₂·2H₂O (8.86 g, 34.7 mmol) and dissolved in EtOH (70 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (50 mL x 2) and H₂O (50 mL). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel EtOAc (Hex = 1/1, R_f = 0.38) to afford a white
- 15 crystal of desired product 14-29 (2.12 g, 69.7 % in 2 steps).

Experiment 14.17**Preparation and Analysis of Compound****Morpholine 14-30**

20

- [0406] Fluorophenyl pyrazole 14-18 (509 mg, 1.69 mmol) was directly weighed into a 5 mL round-bottom flask and dissolved in DMSO (3 mL). The solution was treated with morpholine (295 µL, 3.38 mmol) and heated to 80 °C. After stirring for 2 hrs, the reaction was poured into H₂O (10 mL) and extracted with EtOAc (10 mL x 2). The EtOAc was washed with 1.0 N HCl (5 mL), dried

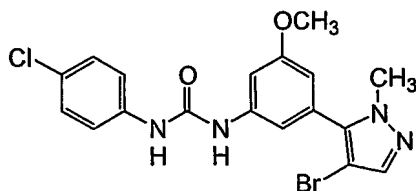
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over MgSO_4 and concentrated under vacuum. The crude product was used for the next step without further purification. A 25 mL round-bottom flask was charged with the crude compound and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.72 g, 6.79 mmol) and dissolved in EtOH (20 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (10 mL x 2) and H_2O (10 mL). The EtOAc was dried over MgSO_4 , concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/1, R_f = 0.45) to afford a white crystal of desired product **14-30** (415 mg, 73.5 % in 2 steps).

Experiment 14.18

10 Preparation and Analysis of Compound

Compound 158



Typical coupling reaction of the precursors and isocyanates:

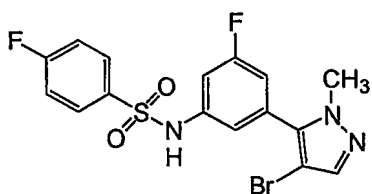
[0407] To a 1 mL oven dried vial, was aniline **14-24** (80 mg, 0.28 mmol, see Experiment 14-11 and Scheme 14-5) dissolved in dichloroethane (0.3 mL) and treated with p-chlorophenyl isocyanate (53 mg, 0.34 mmol) at room temperature.

[0408] After stirring for 12 hrs, the solid was filtered, washed with dichloroethane (0.5 mL) and dried *in vacuo* to afford Compound 158 (90.1 mg, 75%).

20 Experiment 14.19

Preparation and Analysis of Compound

Compound 100



Typical coupling reaction of the precursors and sulfonyl halides or acyl halides

25 [0409] To a 1 mL oven dried vial, was aniline **14-19** (50 mg, 0.17 mmol, see Experiment 14-6 and Scheme 14-3) dissolved in dichloromethane (0.3 mL) and treated with p-fluorophenyl sulfonylchloride (40 mg, 0.20 mmol) and Et_3N (28 μL , 0.21 mmol) at 0 °C. The reaction was warmed

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to room temperature and maintained for 4 hrs. The mixture was poured into H₂O (10 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.52) to afford Compound 100 as a white crystal (58 mg, 85%).:

5

EXAMPLE 15**Experiments 15.1 – 15.22****General Synthetic Strategies, Preparation and Analysis of Compounds**

[0410] Compounds of certain embodiments of the invention were prepared according to the procedures below. The following abbreviations are employed herein:

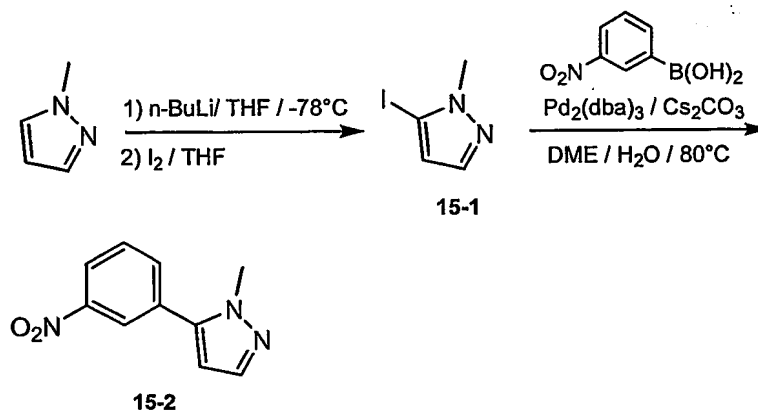
List of Abbreviations:

	DME	Dimethoxyethylene
	THF	Tetrahydrofuran
	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium
15	NCS	N-Chlorosuccinimide
	ACC	1,1-Azobis(cyclohexanecarbonitrile)
	DIEA	Diisopropylethylamine
	DMSO	Dimethylsulfoxide
	Hex	Hexanes
20	EtOAc	Ethyl Acetate

GENERAL SYNTHETIC STRATEGIES

[0411] *N*-Methyl pyrazole was lithiated with *n*-BuLi in THF at -78°C. The lithiated pyrazole was then exchanged with I₂ to form iodopyrazole 15-1 in 78% yield. Suzuki coupling of 1 with 3-nitrophenylboronic acid provided coupled product 15-2 in 67-98% yield (Scheme 15-1).

25

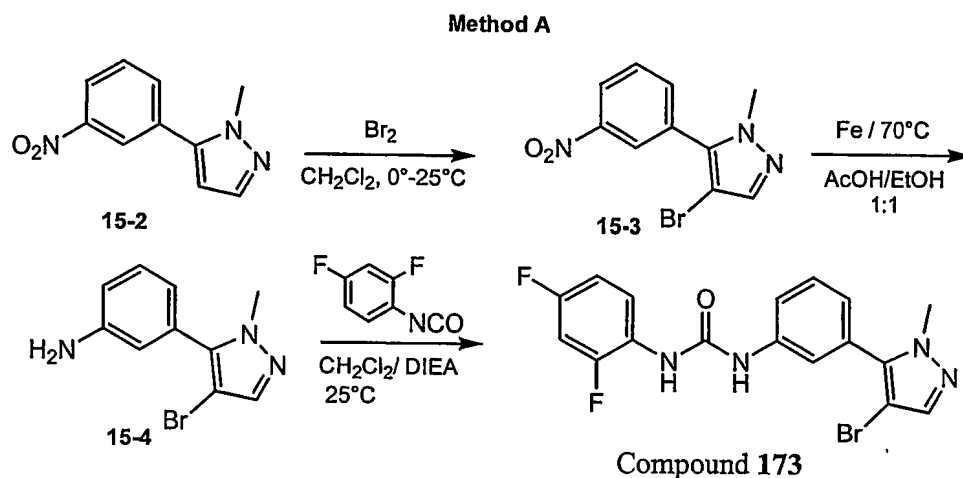


Scheme 15-1

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[0412] Pyrazole 15-2 was brominated at 0°C to provide 15-3 in 68% yield. Intermediate 15-3 was then reduced with iron in 1:1 acetic acid/ethanol to afford aniline 15-4 in 80% yield. Aniline 15-4 was subsequently coupled with 2,4-difluorophenylisocyanate at room temperature to provide Compound 173 in 95% yield (Method A, Scheme 15-2).

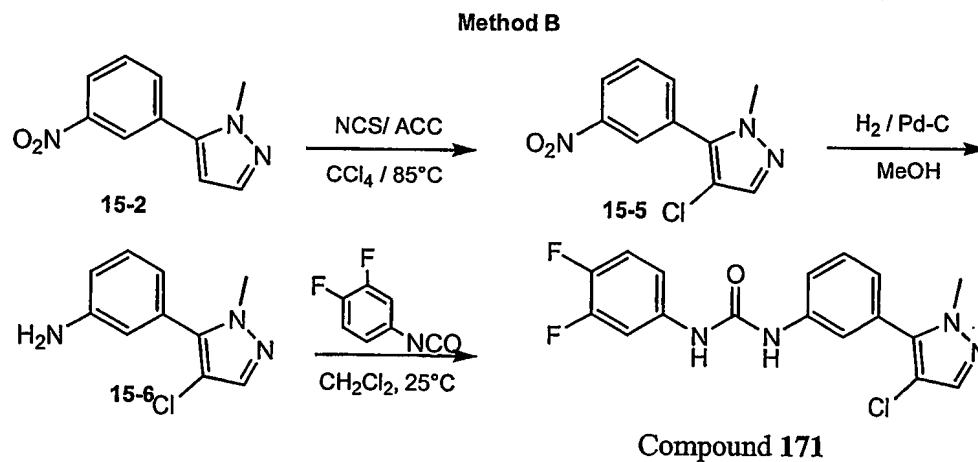
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Scheme 15-2

[0413] Separately, Pyrazole 15-2 was chlorinated at 85°C with NCS providing intermediate chloropyrazole 15-5 in 87% yield. Intermediate 15-5 was then reduced with H₂/Pd-C to provide aniline 15-6 in 88% yield. Aniline 15-6 was subsequently treated with 3,4-difluorophenylisocyanate at room temperature to provide Compound 171 in 85% yield (Method B, Scheme 15-3).

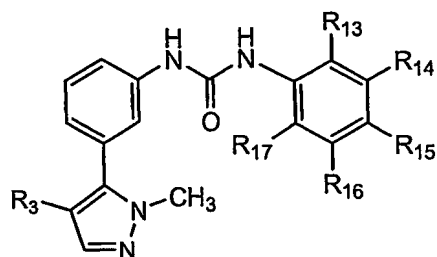
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Scheme 15-3

[0414] The following compounds shown below were made in a similar manner as described above herein for Compound 173 and Compound 171.

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(X)

Compound	R ₃	R ₁₃	R ₁₄	R ₁₅	R ₁₆	R ₁₇	Method
Compound Name							
165	Br	H	F	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea							
166	Br	F	H	H	F	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea							
167	Br	H	F	H	F	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea							
168	Br	H	Cl	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea							
169	Br	CF ₃	H	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea							
170	Br	H	CF ₃	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea							
172	Cl	F	H	H	F	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea							
174	Br	F	F	F	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea							
175	Cl	H	F	H	F	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea							
176	Cl	H	Cl	F	H	H	B
1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea							

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177	Cl	F	H	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea							
178	Cl	F	F	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea							
179	Cl	CF ₃	H	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-phenyl)-urea							
180	Br	CF ₃	H	Cl	H	H	A
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-phenyl)-urea							
181	Br	H	CF ₃	Cl	H	H	A
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-phenyl)-urea							
182	Cl	H	CF ₃	F	H	H	B
1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea							

PREPARATION AND ANALYSIS OF COMPOUNDS

Experiment 15.1

5 Preparation and Analysis of Compound

5-Iodo-1-*N*-methylpyrazole 15-1

[0415] *N*-Methylpyrazole (10.0 mL, 120.6 mmol) was dissolved in THF (250 mL) and treated with *n*-BuLi (75.6 mL, 120.6 mmol) at -78°C under dry N₂. The reaction was stirred for 30 min at -78°C. The reaction mixture was treated at -78°C with I₂ (30.7 gm, 120.6 mmol) in THF (200 mL). The reaction was allowed to warm to room temperature and stirred an additional 3 hours. The mixture was quenched by the addition of NH₄Cl (200 mL) stirring for 30 min. Extraction with EtOAc (3 x 100 mL) then washing of the organic phase with a 10% solution of Na₂S₂O₃ removed the excess I₂. The combined organic layers were then dried over Na₂SO₄, filtered and the solvent removed under reduced pressure to provide 19.6g of 5-Iodo-1-*N*-methylpyrazole 15-1 in 78% yield (the material was used as crude in the next step): LCMS *m/z* 209 MH⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 2 Hz, 1H), 6.4 (d, *J* = 2 Hz, 1H), 3.9 (s, 3H).

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Experiment 15.2**Preparation and Analysis of Compound****Pyrazole 15-2 (Route-1)**

[0416] The intermediate iodopyrazole **15-1** (588 mg, 2.82 mmol) was dissolved in DME (5 mL) and H₂O (500 μ L). To this solution was added 3-nitrophenylboronic acid (943 mg, 5.65 mmol), Cs₂CO₃ (920 mg, 2.82 mmol) and Pd(Ph₃P)₄ (555 mg, 0.48 mmol). The mixture was degassed with argon and heated to 80°C for 12 hours. After cooling to room temperature, brine (30 mL) was added and the mixture extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, Hexanes/EtOAc gradient elution) to provide 562 mg (98%) of pyrazole **15-2** as a pale yellow solid: LCMS m/z 204 MH⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.25 (s, 1H), 8.22 (dd, J=7.8, 1.0 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.64 (dd, J=8.0, 8.0 Hz, 1H), 7.52 (m, 1H), 6.39 (m, 1H), 3.92 (m, 3H).

Pyrazole 15-2 (Route-2)

[0417] The intermediate iodopyrazole **5-1** (17.4 gm, 83.5 mmol) was dissolved in DME (200 mL) and H₂O (1 mL). To this solution was added 3-nitrophenylboronic acid (14.0 gm, 83.5 mmol), Cs₂CO₃ (27.4 gm, 83.5 mmol) and Pd₂(dba)₃ (1.37 gm, 14 mmol). The mixture was degassed with argon and heated to 80°C for 12 hours. After cooling to room temperature, brine (100 mL) was added and the mixture extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, Hexanes/EtOAc gradient elution) to provide 17.1 gm (67%) of Pyrazole **15-2** as a pale yellow solid: LCMS m/z 204 MH⁺. ¹H NMR (400MHz, CDCl₃) δ 8.25 (s, 1H), 8.22 (dd, J=7.8, 1.0 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.64 (dd, J=8.0, 8.0 Hz, 1H), 7.52 (m, 1H), 6.39 (m, 1H), 3.92 (m, 3H).

Experiment 15.3**Preparation and Analysis of Compound****Method A****Bromopyrazole 15-3**

[0418] Pyrazole **15-2** (5.79 g, 28.5 mmol) was dissolved in 150 mL of CH₂Cl₂ and cooled to 0°C. Bromine (5.40 g, 34.2 mmol) in CH₂Cl₂ (55 mL) was added drop wise under argon over 30 minutes. After the addition was complete, the reaction mixture stirred for 3 hours at room temp. The

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reaction mixture was quenched with a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ and 1N NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x200 ml). The organic layers were combined, dried over Na_2SO_4 , and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2 , Hexanes/EtOAc gradient elution) to provide 5.4 gm (68%) of Bromopyrazole 15-3 and 1.1 gm (14%) of unreacted starting material. LCMS m/z (%) = 284 ($\text{M}+\text{H}^{81}\text{Br}$, 100), 282 ($\text{M}+\text{H}^{79}\text{Br}$, 89). ^1H NMR (400MHz, CDCl_3) σ 8.33 (d, $J=6.0$ Hz, 1H), 8.29 (s, 1H), 7.77 (d, $J=8.0$ Hz, 1H), 7.71 (dd, $J=8.0$ Hz, 1H), 7.56 (s, 1H), 3.87 (s, 3H).

Intermediate 15-4:

[0419] A slurry of pyrazole 15-3 (2.05 g, 7.26 mmol) in a 1:1 mixture of acetic acid and ethanol (30 ml) was treated with iron powder (1.62 g, 29.0 mol) and heated to 70°C for 4 hours. The reaction mixture was allowed to cool to room temperature and 1N NaOH (100 ml) was added to form white precipitate (FeOH). EtOAc (100 mL) was added and filtered through celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (2x100 ml). The organic layers were combined and dried over Na_2SO_4 , filtered, and concentrated to afford 1.46 g of 15-4, in 80% yield as a white solid. LCMS m/z (%) = 254 ($\text{M}+\text{H}^{81}\text{Br}$, 100), 252 ($\text{M}+\text{H}^{79}\text{Br}$, 96). ^1H NMR (400MHz, CDCl_3) σ 7.50 (s, 2H), 7.26 (m, 2H), 6.75 (m, 2H), 6.68 (s, 1H), 3.81 (s, 3H).

Experiment 15.4

20 Preparation and Analysis of Compound

Compound 173

[0420] Intermediate 4 (209 mg, 0.83 mmol, see Experiment 15.3) was dissolved in 3 mL of CH_2Cl_2 , treated with 2,4-difluorophenylisocyanate (385 mg, 2.49 mmol), diisopropylethylamine (168 mg, 1.66 mmol), and stirred at room temperature overnight. The solvent was removed under reduced pressure, dissolved in DMSO (5 ml), and purified by preparative HPLC to afford Compound 173 as a white solid, 325 mg, 97% yield: LCMS m/z (%) = 409 ($\text{M}+\text{H}^{81}\text{Br}$, 100), 407 ($\text{M}+\text{H}^{79}\text{Br}$, 97). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) σ 9.20 (s, 1H), 8.55 (s, 1H), 8.04 (m, 1H), 7.64 (m, 1H), 7.59 (s, 1H), 7.51 (d, $J=8.4$ Hz, 1H), 7.44 (dd, $J=7.8$ Hz, 1H), 7.29 (m, 1H), 7.09 (d, $J=7.2$ Hz, 1H), 7.03 (dd, $J=8.8$ Hz, 1H), 3.77 (s, 3H).

30

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Experiment 15.5**Preparation and Analysis of Compound****Compound 165**

- [0421] Intermediate 4 was treated with 3,4-difluorophenylisocyanate, in a similar manner to
5 Compound 173, providing a 99% yield of Compound 165: LCMS m/z (%) = 409 ($M+H^{81}Br$, 100),
407 ($M+H^{79}Br$, 97). 1H NMR (400 MHz, $DMSO-d_6$) σ 8.98 (s, 2H), 7.57 (m, 3H), 7.44 (dd, $J=8.0$ Hz,
1H), 7.36 (d, $J=9.2$ Hz, 1H), 7.31 (d, $J=9.6$ Hz, 1H), 7.10 (m, 2H), 3.78 (s, 3H).

Experiment 15.610 **Preparation and Analysis of Compound****Compound 166**

- [0422] Intermediate 4 was treated with 2,5-difluorophenylisocyanate, in a similar manner to
Compound 173, providing a 76% yield of Compound 166: LCMS m/z (%) = 409 ($M+H^{81}Br$, 100),
407 ($M+H^{79}Br$, 97). 1H NMR (400 MHz, $CDCl_3$) σ 7.93 (m, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 7.57 (s,
15 1H), 7.50 (s, 1H), 7.24 (m, 2H), 7.10 (d, $J=6.8$ Hz, 1H), 6.96 (m, 1H), 6.64 (m, 1H), 3.82 (s, 3H).

Experiment 15.7**Preparation and Analysis of Compound****Compound 167**

- 20 [0423] Intermediate 4 was treated with 3,5-difluorophenylisocyanate, in a similar manner to
Compound 173, after chromatography on silica (Chromatatron, Hex/EtOAc gradient), providing a
45% yield of Compound 167: LCMS m/z (%) = 409 ($M+H^{81}Br$, 100), 407 ($M+H^{79}Br$, 96). 1H NMR
(400 MHz, Acetone- d_6) σ 8.59 (s, 1H), 8.47 (s, 1H), 7.68 (s, 1H), 7.64 (d, $J=8.0$ Hz, 1H), 7.52 (s,
1H), 7.47 (dd, $J=7.8$ Hz, 1H), 7.24 ($J=9.6$ Hz, 2H), 7.14 (d, $J=7.6$ Hz, 1H), 6.61 (dd, $J=8.6$ Hz, 1H),
25 3.83 (s, 3H).

Experiment 15.8**Preparation and Analysis of Compound**30 **Compound 168**

- [0424] Intermediate 4 was treated with 3-chloro-4-fluorophenylisocyanate, in a similar
manner to Compound 173, providing a 91% yield of Compound 168: LCMS m/z (%) = 427
($M+H^{81}Br$, ^{37}Cl , 33), 425 ($M+H^{81}Br$, ^{35}Cl & ^{79}Br , ^{37}Cl , 100), 423 ($M+H^{79}Br$, ^{35}Cl , 63). 1H NMR (400

-168-

MHz. Acetone- d_6) σ 8.41 (s, 1H), 8.37 (s, 1H), 7.87 (m, 1H), 7.69 (m, 1H), 7.62 (d, $J=2.4$ Hz, 1H), 7.52 (s, 1H), 7.45 (dd, $J=7.8$ Hz, 1H), 7.38 (m, 1H), 7.21 (dd, $J=9.0$ Hz, 1H), 7.12 (d, $J=6.8$ Hz, 1H), 3.83 (s, 3H).

5 Experiment 15.9

Preparation and Analysis of Compound

Compound 169

[0425] Intermediate 4 was treated with 2-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound 173, providing a 47% yield of Compound 169: LCMS m/z (%) = 459 (M+H⁸¹Br, 100), 457 (M+H⁷⁹Br, 78). ¹H NMR (400 MHz. DMSO- d_6) σ 9.47 (s, 1H), 8.64 (s, 1H), 8.16 (s, 1H), 7.86 (m, 1H), 7.76 (m, 1H), 7.64 (s, 1H), 7.54 (m, 2H), 7.45 (dd, $J=7.8$ Hz, 1H), 7.09 (d, $J=7.2$ Hz, 1H), 3.77 (s, 3H).

Experiment 15.10

15 Preparation and Analysis of Compound

Compound 170

[0426] Intermediate 4 was treated with 3-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound 173, providing a 56% yield of Compound 170: LCMS m/z (%) = 459 (M+H⁸¹Br, 100), 457 (M+H⁷⁹Br, 82). ¹H NMR (400 MHz. DMSO- d_6) σ 9.13 (s, 1H), 9.04 (s, 1H), 7.98 (m, 1H), 7.64 (m, 2H), 7.58 (s, 1H), 7.55 (d, $J=8.4$ Hz, 1H), 7.45 (m, 2H), 7.09 (d, $J=8.8$ Hz, 1H), 3.77 (s, 3H).

Experiment 15.11

25 Preparation and Analysis of Compound

Compound 174

[0427] Intermediate 4 was treated with 2,3,4-trifluorophenylisocyanate, in a similar manner to Compound 173, providing a 22% yield of Compound 174: LCMS m/z (%) = 427 (M+H⁸¹Br, 100), 425 (M+H⁷⁹Br, 78). ¹H NMR (400 MHz. Acetone- d_6) σ 8.74 (s, 1H), 8.22 (s, 1H), 8.01 (m, 1H), 7.71 (m, 1H), 7.64 (d, $J=8.0$ Hz, 1H), 7.52 (s, 1H), 7.48 (dd, $J=7.8$ Hz, 1H), 7.15 (m, 2H), 3.84 (s, 3H).

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Experiment 15.12**Preparation and Analysis of Compound****Compound 180**

[0428] Intermediate 4 was treated with 2-trifluoromethyl-4-chlorophenylisocyanate, in a similar manner to Compound 173, after chromatography on silica (Biotage, Hex/EtOAc gradient) provided Compound 180 in a 73% yield: LCMS m/z (%) = 477 (M+H⁸¹Br, ³⁷Cl, 40), 475 (M+H⁸¹Br, ³⁵Cl & ⁷⁹Br, ³⁷Cl, 100), 473 (M+H⁷⁹Br, ³⁵Cl, 72). ¹H NMR (400 MHz, Acetone-d₆) σ 9.04 (s, 1H), 8.19 (d, J=9.2 Hz, 1H), 7.77 (s, 1H), 7.66 (m, 4H), 7.52 (s, 1H), 7.48 (dd, J=8.0 Hz, 1H), 7.14 (d, J=7.6, 1H), 3.83 (s, 3H).

10

Experiment 15.13**Preparation and Analysis of Compound****Compound 181**

[0429] Intermediate 4 was treated with 3-trifluoromethyl-4-chlorophenylisocyanate, in a similar manner to Compound 173, providing a 56% yield of Compound 181: LCMS m/z (%) = 477 (M+H⁸¹Br, ³⁷Cl, 34), 475 (M+H⁸¹Br, ³⁵Cl & ⁷⁹Br, ³⁷Cl, 100), 473 (M+H⁷⁹Br, ³⁵Cl, 62). ¹H NMR (400 MHz, Acetone-d₆) σ 8.85 (s, 1H), 8.72 (s, 1H), 8.16 (d, J=2.8 Hz, 1H), 7.77 (s, J=8.8Hz, 1H), 7.71 (s, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.55 (d, J=8.8 Hz, 1H), 7.52 (s, 1H), 7.48 (dd, J=7.8 Hz, 1H), 7.14 (d, J=8.8, 1H), 3.84 (s, 3H).

20

Experiment 15.14**Preparation and Analysis of Compound****Method B:****Chloropyrazole 15-5**

[0430] Pyrazole 15-2 (2.51 g, 12.3 mmol) was dissolved in 70 ml of CCl₄ and heated to 85°C under reflux. *N*-Chlorosuccinimide (1.81 g, 13.6 mmol) and 1,1-Azobis (cyclohexanecarbonitrile) were added and stirred overnight. The reaction mixture was allowed to cool to room temperature then to 0°C and the white precipitate filtered off. The solvent was removed under reduced pressure and purified by flash chromatography (SiO₂, Hexanes/EtOAc gradient elution) to provide 2.54 g, 87% yield of chloropyrazole 15-5. LCMS m/z (%) = 240 (M+H³⁷Cl, 54), 238 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, CDCl₃) σ 8.33 (d, J=8.4 Hz, 1H), 8.31 (s, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.72 (dd, J=7.8 Hz, 1H), 7.55 (s, 1H), 3.87 (s, 3H).

30

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Intermediate 15-6:

[0431] A slurry of the chloropyrazole 15-5 (973 mg, 4.09 mmol) was reduced at 55 psi H₂ / Pd-C for 4 hours to provide 749 mg of intermediate 15-6 in 88% yield. LCMS m/z (%) = 210 (M+H³⁷Cl, 68), 208 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, CDCl₃) σ 7.47 (s, 2H), 7.29 (s, 1H), 7.25 (dd, J=3.8 Hz, 1H), 6.77 (d, J=2.0 Hz, 1H), 6.75 (d, J=2.0 Hz, 1H), 6.7 (m, 1H), 3.81 (s, 3H).

Experiment 15.15

Preparation and Analysis of Compound

Compound 171

[0432] Intermediate 15-6 (200 mg, 0.96 mmol) was dissolved in 3 mL of CH₂Cl₂, treated with 3,4-difluorophenylisocyanate (4.49 mg, 2.89 mmol), diisopropylethylamine (194 mg, 1.92 mmol), and stirred at room temperature overnight. The solvent was removed under reduced pressure, dissolved in DMSO (5 ml), and purified by preparative HPLC to afford Compound 171 as a white solid, 298 mg, 85% yield: LCMS m/z (%) = 365 (M+H³⁷Cl, 27), 363 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, DMSO-d₆) σ 8.95 (m, 2H), 7.62 (m, 3H), 7.52 (d, J=8.0 Hz, 1H), 7.45 (dd, J=7.8 Hz, 1H), 7.32 (m, 1H), 7.10 (m, 2H), 3.77 (s, 3H).

Experiment 15.16

Preparation and Analysis of Compound

Compound 172

[0433] Intermediate 6 was treated with 2,5-difluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 57% yield of Compound 172: LCMS m/z (%) = 365 (M+H³⁷Cl, 32), 363 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, CD₃OD) σ 7.99 (m, 1H), 7.63 (s, 1H), 7.49 (m, 2H), 7.44 (dd, J=8.0 Hz, 1H), 7.10 (m, 3H), 6.69 (m, 2H), 3.81 (s, 3H).

Experiment 15.17

Preparation and Analysis of Compound

Compound 175

[0434] Intermediate 6 was treated with 3,5-difluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 20% yield of Compound 175: LCMS m/z (%) = 365 (M+H³⁷Cl, 27), 363 (M+H³⁵Cl, 100). ¹H NMR (400 MHz,

-171-

CDCl_3) σ 7.50 (s, 1H), 7.44 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.25 (s, 2H), 7.14 (m, 1H), 6.98 (d, $J=6.8$ Hz, 2H), 6.49 (m, 1H), 3.82 (s, 3H).

Experiment 15.18**5 Preparation and Analysis of Compound****Compound 176**

[0435] Intermediate 6 was treated with 3-chloro-4-fluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 21% yield of Compound 176: LCMS m/z (%) = 383 ($M+H^{37}\text{Cl}, ^{37}\text{Cl}$, 19), 381 ($M+H^{37}\text{Cl}, ^{35}\text{Cl}$, 73),
10 379 ($M+H^{35}\text{Cl}, ^{35}\text{Cl}$, 100). ^1H NMR (400 MHz, CDCl_3) σ 7.50 (m, 2H), 7.43 (m, 2H), 7.25 (s, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 7.06 (dd, $J=8.6$ Hz, 1H), 6.99 (s, 1H), 6.95 (s, 1H), 3.82 (s, 3H).

Experiment 15.19**Preparation and Analysis of Compound****15 Compound 177**

[0436] Intermediate 6 was treated with 2,4-difluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 37% yield of Compound 177: LCMS m/z (%) = 365 ($M+H^{37}\text{Cl}$, 32), 363 ($M+H^{35}\text{Cl}$, 100). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) σ 9.20 (s, 1H), 8.55 (s, 1H), 8.04 (m, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.50 (d, $J=5.6$ Hz, 1H),
20 7.44 (dd, $J=7.8$, 1H), 7.29 (m, 1H), 7.09 (d, $J=6.0$, 1H), 7.03 (dd, $J=8.8$, 1H), 3.77 (s, 3H).

Experiment 15.20**Preparation and Analysis of Compound****Compound 178**

25 [0437] Intermediate 6 was treated with 2,3,4-trifluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 45% yield of Compound 178: LCMS m/z (%) = 383 ($M+H^{37}\text{Cl}$, 52), 381 ($M+H^{35}\text{Cl}$, 100). ^1H NMR (400 MHz, $\text{Acetone}-d_6$) σ 8.68 (s, 1H), 8.17 (s, 1H), 8.02 (m, 2H), 7.72 (s, 1H), 7.63 (d, $J=7.2$ Hz, 1H), 7.51 (s, 1H), 7.48 (d, $J=8.4$ Hz, 1H), 7.16 (m, 1H), 3.83 (s, 3H).

30

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Experiment 15.21**Preparation and Analysis of Compound****Compound 179**

[0438] Intermediate 6 was treated with 2-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound 171, after chromatography on silica (Biotage, Hex/EtOAc gradient) providing a 32% yield of Compound 179: LCMS (%) = 415 (M+H³⁷Cl, 48), 413 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, Acetone-d₆) δ 8.92 (s, 1H), 8.15 (s, 1H), 8.07 (dd, J=6.8 Hz, 1H), 7.96 (m, 1H), 7.72 (m, 1H), 7.62 (d, J=7.6 Hz, 1H), 7.49 (m, 3H), 7.14 (d, J=7.6 Hz, 1H), 3.82 (s, 3H).

Experiment 15.22**Preparation and Analysis of Compound****Compound 182**

[0439] Intermediate 4 was treated with 3-trifluoromethyl-4-fluorophenylisocyanate, in a similar manner to Compound 171, providing a 71% yield of Compound 182: LCMS m/z (%) = 415 (M+H³⁷Cl, 79), 413 (M+H³⁵Cl, 100). ¹H NMR (400 MHz, Acetone-d₆) δ 8.50 (s, 1H), 8.45 (s, 1H), 8.04 (d, J=8.8 Hz, 1H), 7.76 (m, 1H), 7.71 (s, 1H), 7.62 (d, J=8.0 Hz, 1H), 7.51 (s, 1H), 7.48 (dd, J=7.8 Hz, 1H), 7.33 (dd, J=9.6 Hz, 1H), 7.15 (d, J=7.2 Hz, 1H), 3.83 (s, 3H).

EXAMPLE 16**Experiments 16.1 – 16.5****General Synthetic Strategies, Preparation and Analysis of Compounds**

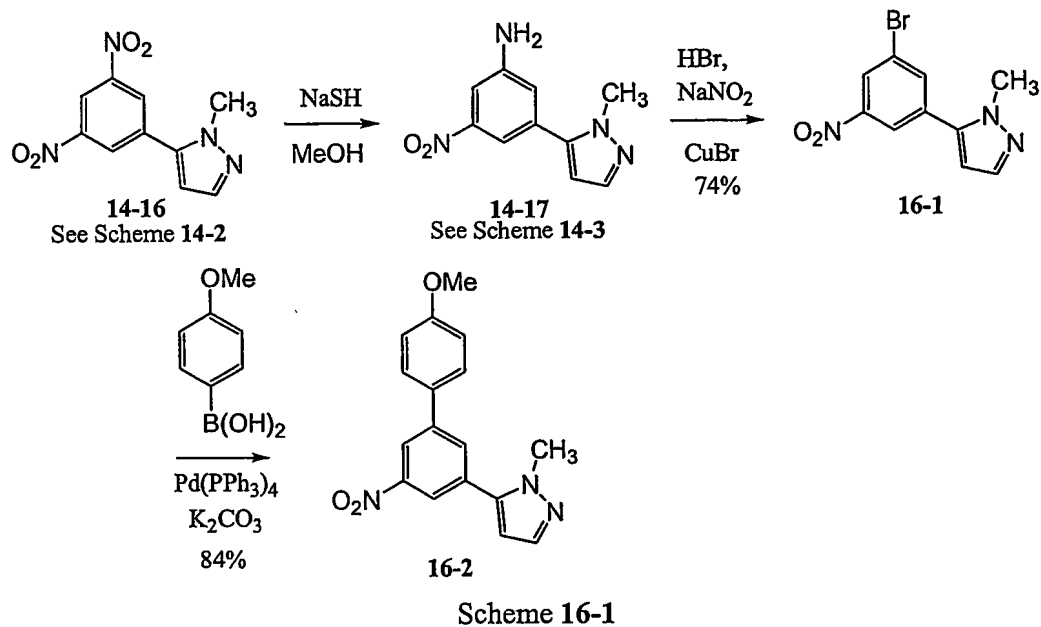
[0440] Compounds of certain embodiments of the invention were prepared according to the procedures below.

General Synthetic Strategies

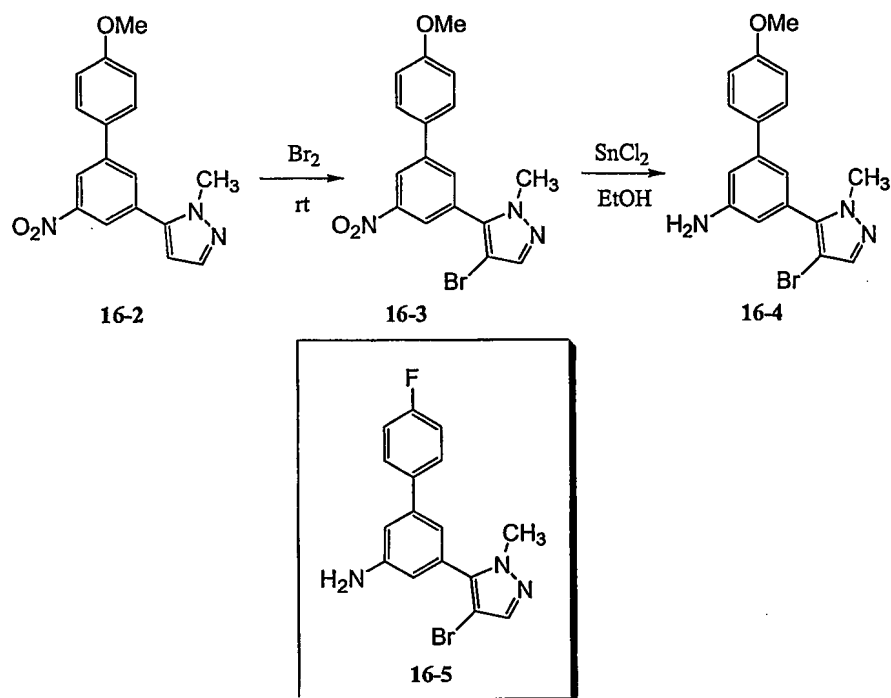
[0441] Various aryl functionalities were introduced on the phenyl ring. By way of example, dinitro 14-15 (see Scheme 14-2) was reduced with NaSH in ethanol under reflux conditions, followed by bromination under Sandmeyer's conditions to afford Aryl bromide 16-1 in 56 % yield (2 steps). Aryl bromide 16-1 was coupled with *p*-methoxyphenyl boronic acid with Pd(PPh₃)₄ and K₂CO₃ as a base in dioxane to furnish the coupled product 16-2 (Scheme 16-1). The reaction was very clean and the desired product was purified by recrystallization in ethanol. Coupled product 16-2 was subsequently brominated with Br₂ in dichloromethane at room temperature (i.e., 16-3) followed by

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reduction with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in Ethanol to furnish the aniline precursor 16-4. 4-Fluorophenyl functionality was also introduced on the ring in a similar manner (Scheme 16-2).



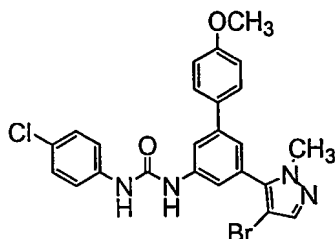
5



Scheme 16-2

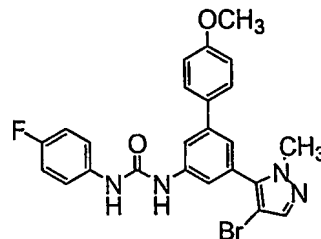
[0442] Anilines **16-4** and **16-5** were coupled with various isocyanates, acyl halides and sulfonyl halides to form urea, amide and sulfonamide type molecules respectively in good yields. The tables of the new compounds are shown below (TABLES 16-1 and 16-2).

5 **TABLE 16-1** Compounds of the invention containing *p*-methoxyphenyl functionality.



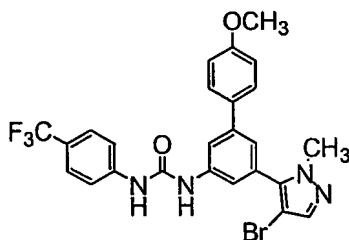
Compound 191

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea



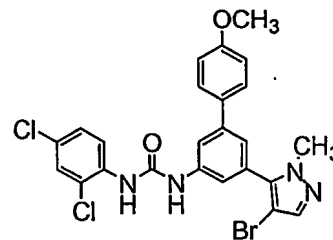
Compound 192

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea



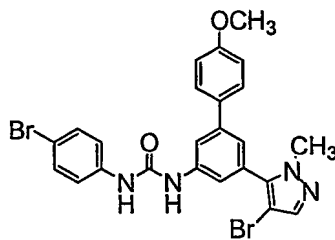
Compound 186

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea



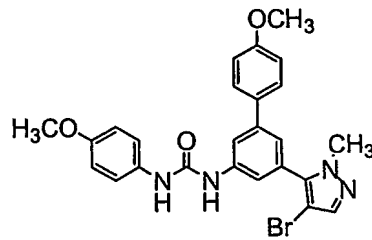
Compound 187

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea



Compound 200

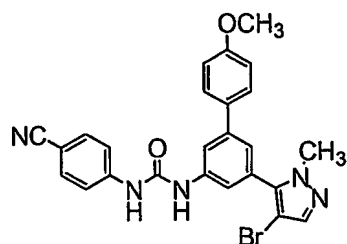
1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea



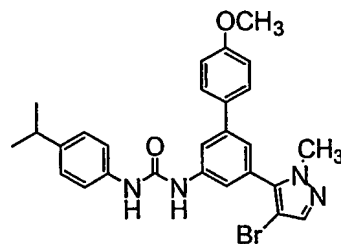
Compound 198

1-[5-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea

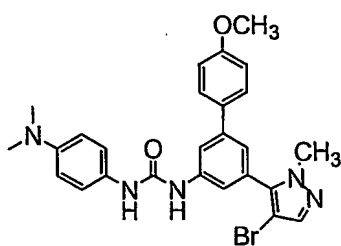
-175-

**Compound 196**

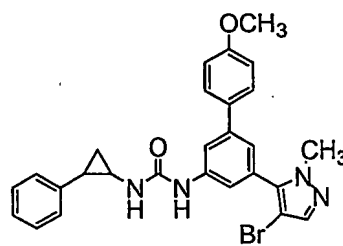
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea

**Compound 201**

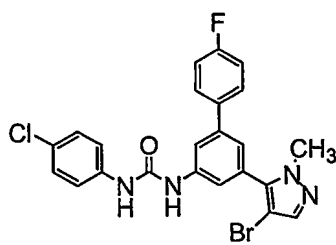
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea

**Compound 185**

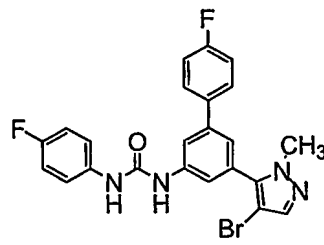
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea

**Compound 202**

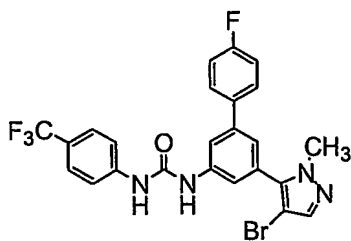
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea

TABLE 16-1 Compounds of the invention containing *p*-fluorophenyl functionality.**Compound 199**

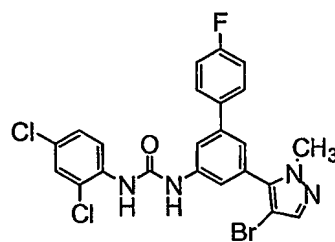
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea

**Compound 204**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea

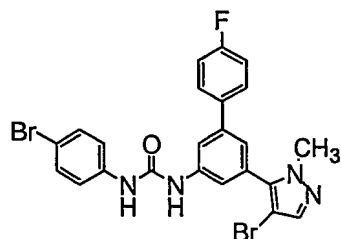
**Compound 190**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea

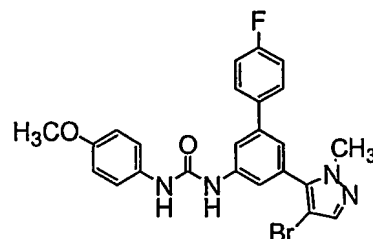
**Compound 194**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea

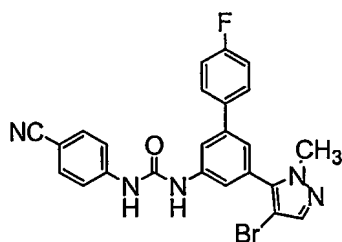
-176-

**Compound 197**

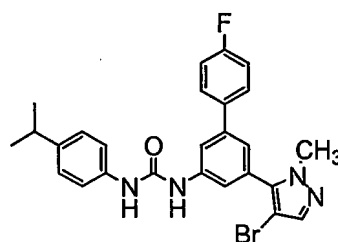
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea

**Compound 188**

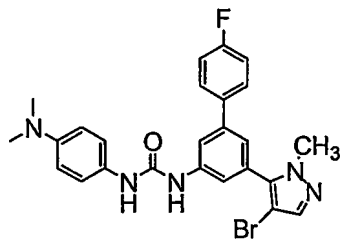
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea

**Compound 193**

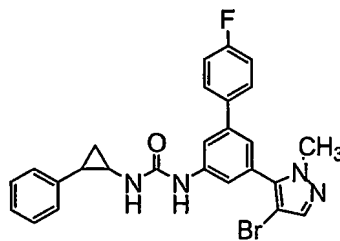
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea

**Compound 195**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea

**Compound 189**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea

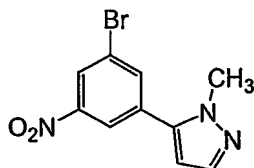
**Compound 203**

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea

5 Experiment 16.1

Preparation and Analysis of Compound

Aryl bromide 16-1:



[0443] Aniline 14-17 (9.89 g, 39.9 mmol, Experiment 14.4 and Scheme 14-3) was dissolved
10 in MeOH (150 mL) and toluene (50 mL) and refluxed to dissolve all solids. NaSH (6.0 g, 107.7

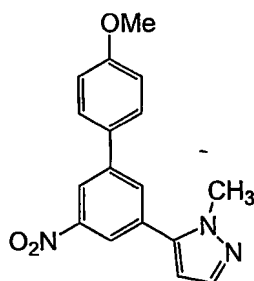
-177-

mmol) in MeOH (50 mL) was added into the solution for 45 min. The reaction mixture was stirred for 30 min at the same temperature and cooled to room temperature. The reaction mixture was concentrated under vacuum and dissolved in EtOAc (250 mL). The EtOAc was washed with H₂O (100 mL x 2), dried over MgSO₄ and concentrated to afford crude Aniline 14-17. The crude compound was used for the next step without further purification. The crude Aniline 14-17 was added into 45% HBr (50 mL) at 0 °C and warmed to room temperature. After stirring for 30 min, the solution was cooled to -30 °C and NaNO₂ (2.75 g, 39.9 mmol) added portionwise for 10 min. The reaction mixture was maintained at the same temperature for 30 min. The mixture was heated to 100 °C and stirred for 10 min. The reaction mixture was cooled to room temperature and quenched with crushed ice (250 g). The crude product was extracted with EtOAc (250 mL), dried over MgSO₄ and concentrated under vacuum. The crude material was purified by column chromatograph (EtOAc/Hex = 1/1, R_f = 0.85) to afford the desired product as a white crystal Aryl bromide 16-1 (5.8 g, 52.1 % in 2 steps).

15 Experiment 16.2

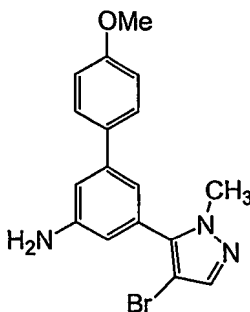
Preparation and Analysis of Compound

Biaryl 16-2:



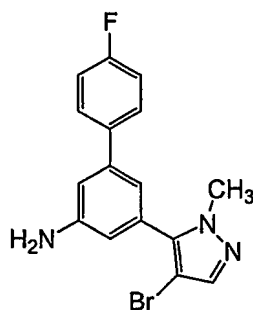
[0444] Aryl bromide 16-1 (700 mg, 2.5 mmol), *p*-methoxyphenyl boronic acid (380 mg, 2.5 mmol) and Pd(PPh₃)₄ (289 mg, 0.25mmol) were directly weighed into a 25 mL round-bottom flask and dissolved in dioxane (10 mL). The solution was treated with K₂CO₃ (760 mg, 5.5 mmol) in H₂O (2.75 mL) and heated to 80 °C. After stirring for 4 hrs, the reaction was poured into H₂O (50 mL) and extracted with EtOAc (20 mL x 2). The EtOAc was dried over MgSO₄ and concentrated under vacuum. The residue was purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.64) to afford Biaryl 16-2 as a white crystal (649 mg, 84.2%).:

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Experiment 16.3**Preparation and Analysis of Compound****Amino biaryl 16-4:**

- 5 [0445] To the solution of Biaryl 16-2 (618 mg, 2.0 mmol) in dichloromethane (5 mL), was added dropwise Br₂ (128 μL, 2.5 mmol) in dichloromethane (1 mL) for 5 min at 0 °C. After addition of Br₂, the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H₂O (10 mL), concentrated under vacuum and triturated in EtOH to afford yellowish crystals. A 5 mL round-bottom flask was charged with the solids and SnCl₂•2H₂O (2.61 g, 10.0 mmol) and dissolved in EtOH (5 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (20 mL x 2) and H₂O (20 mL). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.25) to afford the desire Amino biaryl 16-4 as white crystals (583 mg, 82% in 2 steps).

15

Experiment 16.4**Preparation and Analysis of Compound****Amino biaryl 16-5:**

- 20 [0446] Aryl bromide 16-1 (1.28 g, 4.57 mmol), *p*-fluorophenyl boronic acid (700 mg, 5.0 mmol) and Pd(PPh₃)₄ (578 mg, 0.5 mmol) were directly weighed into a 50 mL round-bottom flask and dissolved in dioxane (30 mL). The solution was treated with K₂CO₃ (1.38 g, 10.0 mmol) in H₂O (5.43 mL) and heated to 80 °C. After stirring for 4 hrs, the reaction was poured into H₂O (50 mL) and

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extracted with EtOAc (30 mL x 2). The EtOAc was dried over MgSO₄ and concentrated under vacuum. The residue was dissolved in dichloromethane (25 mL), and Br₂ (282 μ L, 5.5 mmol) in dichloromethane (3 mL) was added dropwise for 5 min at 0 °C. After addition of Br₂, the reaction mixture was warmed to room temperature and stirred for 2 hrs. The reaction mixture was washed with H₂O (20 mL), concentrated under vacuum and triturated in EtOH to afford yellowish crystals. A 5 mL round-bottom flask was charged with the solids and SnCl₂•2H₂O (4.12 g, 18.3 mmol) and dissolved in EtOH (20 mL). The mixture was refluxed for 1.5 hrs and cooled to room temperature. The reaction was concentrated under vacuum and extracted with EtOAc (20 mL x 2) and H₂O (20 mL). The EtOAc was dried over MgSO₄, concentrated under vacuum and purified over silica gel (EtOAc/Hex = 1/2, R_f = 0.31) to afford Amino biaryl 16-5 as white crystals (1.31 g, 83 % in 3 steps).

[0447] In general, the coupling procedures disclosed herein between an amine, such as, Amino biaryls 16-5, 16-5 and the like, with isocyanates, acid halides and sulfonyl halides can be utilized to achieve the desired urea, amide or sulfonamide products respectively. Analytical data for certain representative compounds, such as those compounds in TABLES 16-1 and 16-2, can be seen in TABLE 16-3 below:

TABLE 16-3
Analytical Data for Representative Compounds
of the Invention

Compound No.	Expected	Found (M+H ⁷⁹ Br)	Found (M+H ⁸¹ Br)
185	520	520	522
186	545	545	547
187	545	545	547
191	511	511	513
192	495	495	497
196	502	502	504
198	507	507	509
200	557	557	559
201	519	519	521
202	517	517	519

20

[0448] An important point that can be derived from the foregoing data is that by using a constitutively activated form of the receptor in the direct identification of candidate compounds, the selectivity of the compounds is exceptional: as those in the art appreciate, the homology between the human 5-HT_{2A} and 5-HT_{2C} receptors is about 95%, and even with such homology, certain of the directly identified compounds, e.g., Compounds 8 and 9 evidence a 100-fold difference in selectivity preference (as measured by IC₅₀ values) for the 5-HT_{2A} receptor compared with the 5-HT_{2C} receptor.

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This is important for pharmaceutical compositions in that such selectivity can help to reduce side-effects associated with interaction of a drug with a non-target receptor.

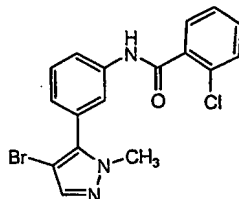
[0449]

Different embodiments of the invention will consist of different constitutively activated receptors, different expression systems, different assays, and different compounds. Those skilled in the art will understand which receptors to use with which expression systems and assay methods. All are considered within the scope of the teaching of this invention.

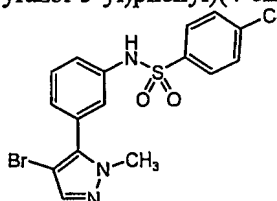
[0450]

In some embodiments of each of the genera disclosed in this specification, the following compounds (a) through (k), and combinations or subcombinations thereof, are included therein:

- 10 (a) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-chlorophenyl)carboxamide;

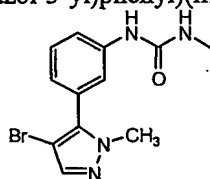


- (b) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl)sulfonamide;

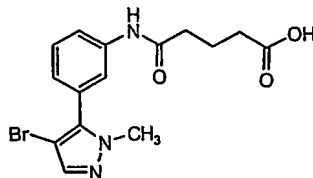


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- (c) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(methylamino)carboxamide;



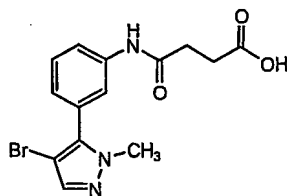
- (d) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((3-carboxy-prop-1-yl)carboxamide;



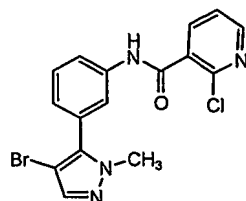
20

- (e) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-carboxy-eth-1-yl)carboxamide;

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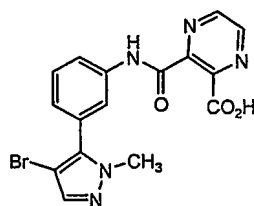


(f) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-chloro-3-pyridyl)carboxamide;



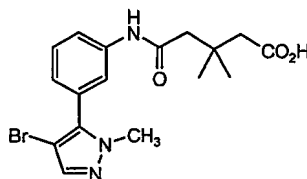
5

(g) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((3-carboxy-pyrazin-2-yl)carboxamide;

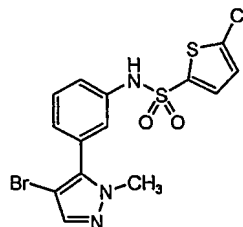


10

(h) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((2-methyl-1-carboxy-prop-2-yl)carboxamide;

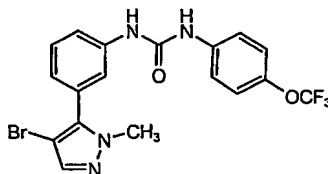


(i) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((5-chlorothiophen-2-yl)sulfonamide;



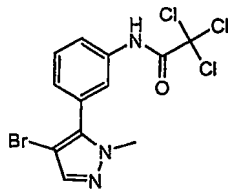
15

(j) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl) amino) carboxamide;



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(k) N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(trichloromethyl)carboxamide.



5

[0451] In some embodiments of each of the general disclosed in this specification, compounds (a) through (k) above, and combinations or subcombinations thereof, are not included therein.

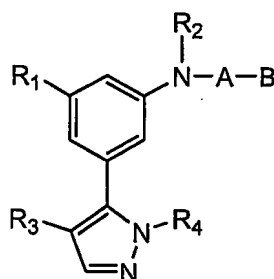
10. [0452] Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety. :

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CLAIMS

We claim:

1. A compound of Formula (I):



(I)

wherein:

i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl;

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R_{10} is H or C_{1-6} alkyl;

R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

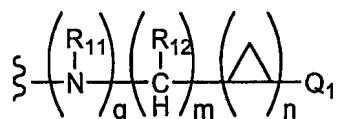
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is $C(=O)$, $C(=S)$ or SO_2 ;

vi) B is L_1 or L_2 ;

L_1 is:



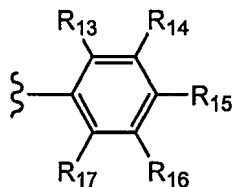
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_{10} ,

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54 NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl,
55 alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be
56 optionally substituted with up to four alkyl substituents in any position;
57

58 L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl,
59 C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said
60 cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to
61 four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃,
62 where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl,
63 alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted
64 with up to four alkyl substituents in any position; or
65 a pharmaceutically acceptable salt.

1 2. The compound of claim 1 wherein B is L₁, q is 1, m is 0, and n is 0.

1 3. The compound of claim 1 wherein B is L₁, q is 1, m is 1, and n is 0.

1 4. The compound of claim 1 wherein B is L₁, q is 1, m is 0, and n is 1.

1 5. The compound of claim 1 wherein B is L₁, q is 0, m is 0, and n is 0.

1 6. The compound of claim 1 wherein B is L₂.

1 7. The compound of claim 2 wherein A is C(=O).

1 8. The compound of claim 3 wherein A is C(=O).

1 9. The compound of claim 4 wherein A is C(=O).

1 10. The compound of claim 5 wherein A is C(=O).

1 11. The compound of claim 2 wherein A is C(=S).

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- 1 12. The compound of claim 3 wherein A is C(=S).
- 1 13. The compound of claim 4 wherein A is C(=S).
- 1 14. The compound of claim 5 wherein A is C(=S).
- 1 15. The compound of claim 5 wherein A is SO₂.
- 1 16. The compound of claim 1 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 17. The compound of claim 1 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 18. The compound of claim 7 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 19. The compound of claim 7 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 20. The compound of claim 8 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 21. The compound of claim 8 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 22. The compound of claim 9 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.

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- 1 23. The compound of claim 9 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 24. The compound of claim 1 wherein R₂ is H and R₄ is methyl.
- 1 25. The compound of claim 16 wherein R₂ is H and R₄ is methyl.
- 1 26. The compound of claim 17 wherein R₂ is H and R₄ is methyl.
- 1 27. The compound of claim 18 wherein R₂ is H and R₄ is methyl.
- 1 28. The compound of claim 19 wherein R₂ is H and R₄ is methyl.
- 1 29. The compound of claim 20 wherein R₂ is H and R₄ is methyl.
- 1 30. The compound of claim 21 wherein R₂ is H and R₄ is methyl.
- 1 31. The compound of claim 22 wherein R₂ is H and R₄ is methyl.
- 1 32. The compound of claim 23 wherein R₂ is H and R₄ is methyl.
- 1 33. The compound of any of claims 25 through 32 wherein R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each
2 independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl,
3 isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH₂ or NO₂.
- 1 34. The compound of claim 15 wherein R₂ is H and R₄ is methyl.
- 1 35. The compound of claim 34 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 36. The compound of claim 6 wherein A is (C=O).

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- 1 37. The compound of claim 36 wherein R₄ is methyl.
- 1 38. The compound of claim 37 wherein R₂ is H.
- 1 39. The compound of claim 38 wherein Q₁ is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl,
2 butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-
3 methoxyphenyl, 2-chlorophenyl, -C(CH₃)=CH, 1-(N-pyridyl)ethyl, or 9-fluorenylmethyl.
- 1 40. The compound of claim 39 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃; and R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
3 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
4 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 41. A compound of claim 1 selected from the group consisting of
2 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
3 1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
4 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;
5 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea;
6 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea;
7 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;
8 4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester;
9 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea;
10 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
11 1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
12 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester;
13 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester;
14 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9H-fluoren-9-ylmethyl
15 ester;
16 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester;
17 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester;
18 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester;

[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl ester;
[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester;
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid methyl ester;
1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-phenyl)-urea;
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;
1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea;
1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-phenyl}-urea;
1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea;
5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid;
1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea;

- 52 1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
53 1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea;
54 1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
55 1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
56 1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea;
57 1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
58 1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
59 1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;
60 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea;
61 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-
62 benzenesulfonamide;
63 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea;
64 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea;
65 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea;
66 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea;
67 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea;
68 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-
69 benzenesulfonamide;
70 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-
71 urea;
72 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-
73 phenyl)-urea;
74 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-
75 urea;
76 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-
77 phenyl)-urea;
78 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide;
79 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-
80 phenyl)-urea;
81 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-
82 dimethylamino-phenyl)-urea;
83 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-
84 phenyl)-urea;

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1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-bromo-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-trifluoromethoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-thiourea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluoro-benzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chloro-benzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichloro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenyl-cyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea;

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- 117 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-
118 urea;
- 119 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-
120 urea;
- 121 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-
122 phenyl)-urea;
- 123 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-
124 urea;
- 125 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-
126 phenyl-cyclopropyl)-urea;
- 127 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-
128 dichloro-phenyl)-urea;
- 129 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-
130 trifluoromethyl-phenyl)-urea;
- 131 1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-
132 yl-phenyl]-urea;
- 133 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-
134 phenyl)-urea;
- 135 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-
136 phenyl)-urea;
- 137 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-
138 urea;
- 139 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-
140 urea;
- 141 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-
142 cyclopropyl)-urea;
- 143 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-
144 urea;
- 145 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-
146 phenyl)-urea;
- 147 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-
148 urea;

- 149 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-
150 benzenesulfonamide;
- 151 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-
152 benzenesulfonamide;
- 153 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-
154 phenyl)-urea;
- 155 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-
156 dimethylamino-phenyl)-urea;
- 157 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-
158 phenyl)-urea;
- 159 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea;
- 160 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-
161 urea;
- 162 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea;
- 163 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-
164 benzenesulfonamide;
- 165 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-
166 phenyl)-urea;
- 167 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea;
- 168 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-
169 benzenesulfonamide;
- 170 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-
171 urea;
- 172 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea;
- 173 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea;
- 174 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-
175 urea;
- 176 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-
177 trifluoromethyl-phenyl)-urea;
- 178 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-
179 urea;
- 180 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-
181 urea;

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182 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea
 183 and
 184 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea.

1 42. A compound of claim 1 selected from the group consisting of:
 2 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea;
 3 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
 4 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;
 5 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea;
 6 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-
 7 phenyl)-urea;
 8 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-
 9 phenyl)-urea;
 10 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
 11 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
 12 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;
 13 1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
 14 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea;
 15 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
 16 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-
 17 phenyl)-urea;
 18 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-
 19 phenyl)-urea;
 20 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-
 21 phenyl)-urea
 22 and
 23 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea.

1 43. The compound of claim 1 selected from the group consisting of:
 2 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;
 3 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;
 4 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)
 5 phenyl)amino)carboxamide;

6 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)
7 phenyl)methyl)amino)carboxamide;
8 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;
9 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;
10 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;
11 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;
12 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;
13 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;
14 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;
15 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;
16 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;
17 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;
18 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;
19 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;
20 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-
21 (trifluoromethoxy)phenyl)carboxamide;
22 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;
23 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;
24 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;
25 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl)
26 phenyl)carboxamide;
27 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;
28 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;
29 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)
30 phenyl)carboxamide;
31 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;
32 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;
33 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-
34 (trifluoromethoxy)phenyl)-carboxamide;
35 N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;
36 N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-
37 yl)phenyl)amino)carboxamide;

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38 N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-
 39 yl)phenyl)amino)carboxamide;
 40 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 41 (trifluoromethylthio)phenyl)carboxamide;
 42 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;
 43 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;
 44 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;
 45 2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;
 46 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;
 47 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;
 48 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 49 fluorophenylmethyl)carboxamide;
 50 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-
 51 dimethoxyphenylmethyl)carboxamide;
 52 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-
 53 trimethoxyphenylmethyl)carboxamide;
 54 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl)
 55 amino)carboxamide;
 56 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 57 methoxyphenylmethyl)carboxamide
 58 and
 59 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide.

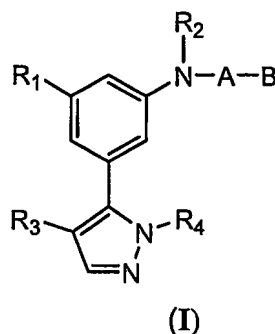
1 44. The compound of claim 1 selected from the group consisting of:
 2 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-
 3 phenyl)-urea;
 4 1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-
 5 urea;
 6 3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea;
 7 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-
 8 phenyl)-urea;
 9 3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea;
 10 3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea

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and

3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea.

45. A compound of Formula (I):



wherein:

i) R_1 is H, halogens, NR_5R_6 , OH or OR_7 , wherein

R_5 and R_6 are independently H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_8R_9$, NR_8R_9 , $NHCOCH_3$, OCF_3 , SMe, $COOR_{10}$, SO_3R_8 , $SO_2NR_8R_9$, COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl wherein each of the C_{3-6} cycloalkyl, C_{1-6} alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, $CONR_8R_9$, NR_8R_9 , $NHCOCH_3$, OCF_3 , SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10} , COMe, COEt, CO-lower alkyl, SCF_3 , CN, C_{2-6} alkenyl, H, halogens, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-6} alkyl, and aryl; or

R_5 and R_6 may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF_3 , CCl_3 , Me, NO_2 , OH, OMe, OEt, OCF_3 , SMe, $COOR_{10}$, $SO_2NR_8R_9$, SO_3R_{10} , $NHCOCH_3$, COEt, COMe, or halogen;

R_8 and R_9 are independently a H, or C_{1-6} alkyl, or C_{2-6} alkenyl, or cycloalkyl, or aryl, or CH_2 aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF_3 , OCF_3 , OEt, CCl_3 , Me, NO_2 , OH, OMe, SMe, COMe, CN, $COOR_{10}$, SO_3R_{10} , COEt, $NHCOCH_3$, or aryl;

R_{10} is H or C_{1-6} alkyl;

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R_7 is H or C_{1-6} alkyl;

ii) R_2 is H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

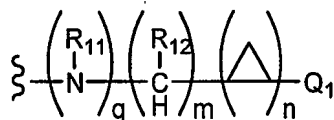
iii) R_3 is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

v) A is $C(=O)$, $C(=S)$ or SO_2 ;

vi) B is L_1 or L_2 ;

L_1 is:



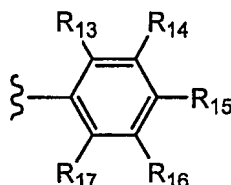
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R_{11} and R_{12} are each independently H, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, or cycloalkyl;

Q_1 is:



wherein:

R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each independently H, halogen, CN, NR_8R_9 , $COOR_{10}$, SR_{10} , straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_{10} , NR_8R_9 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, and said cycloalkyl, aryl,

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alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L_2 is $-O-Q_2$ wherein Q_2 is straight chain or branched C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO_2 , OR_7 , halogen, $-C(p)_3$, or $-O-C(p)_3$ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt; provided that the compound is not any of the following 43 compounds:

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl)amino)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl)methyl)amino)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(trifluoromethoxy)phenyl)carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;

((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;

- 88 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;
89 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl)
90 phenyl)carboxamide;
91 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;
92 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;
93 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)
94 phenyl)carboxamide;
95 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;
96 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;
97 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-
98 (trifluoromethoxy)phenyl)-carboxamide;
99 N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;
100 N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-
101 yl)phenyl)amino)carboxamide;
102 N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-
103 yl)phenyl)amino)carboxamide;
104 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
105 (trifluoromethylthio)phenyl)carboxamide;
106 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;
107 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;
108 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;
109 2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;
110 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;
111 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;
112 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
113 fluorophenylmethyl)carboxamide;
114 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-
115 dimethoxyphenylmethyl)carboxamide;
116 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-
117 trimethoxyphenylmethyl)carboxamide;
118 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl)
119 amino)carboxamide;

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120 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
121 methoxyphenylmethyl)carboxamide
122 and
123 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-methoxy)phenylethyl)carboxamide.

1 46. The compound of claim 45 wherein B is L₁, q is 1, m is 0, and n is 0.

1 47. The compound of claim 45 wherein B is L₁, q is 1, m is 1, and n is 0.

1 48. The compound of claim 45 wherein B is L₁, q is 1, m is 0, and n is 1.

1 49. The compound of claim 45 wherein B is L₁, q is 0, m is 0, and n is 0.

1 50. The compound of claim 45 wherein B is L₂.

1 51. The compound of claim 46 wherein A is C(=O).

1 52. The compound of claim 47 wherein A is C(=O).

1 53. The compound of claim 48 wherein A is C(=O).

1 54. The compound of claim 49 wherein A is C(=O).

1 55. The compound of claim 46 wherein A is C(=S).

1 56. The compound of claim 47 wherein A is C(=S).

1 57. The compound of claim 48 wherein A is C(=S).

1 58. The compound of claim 49 wherein A is C(=S).

1 59. The compound of claim 49 wherein A is SO₂.

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- 1 60. The compound of claim 45 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 61. The compound of claim 45 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 62. The compound of claim 51 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 63. The compound of claim 51 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 64. The compound of claim 52 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 65. The compound of claim 52 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 66. The compound of claim 53 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-
2 yl, 4-methylpiperazin-1-yl, OH or OCH₃.
- 1 67. The compound of claim 53 wherein R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.
- 1 68. The compound of claim 45 wherein R₂ is H and R₄ is methyl.
- 1 69. The compound of claim 60 wherein R₂ is H and R₄ is methyl.
- 1 70. The compound of claim 61 wherein R₂ is H and R₄ is methyl.

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- 1 71. The compound of claim 62 wherein R_2 is H and R_4 is methyl.
- 1 72. The compound of claim 63 wherein R_2 is H and R_4 is methyl.
- 1 73. The compound of claim 64 wherein R_2 is H and R_4 is methyl.
- 1 74. The compound of claim 65 wherein R_2 is H and R_4 is methyl.
- 1 75. The compound of claim 66 wherein R_2 is H and R_4 is methyl.
- 1 76. The compound of claim 67 wherein R_2 is H and R_4 is methyl.
- 1 77. The compound of any of claims 69 through 76 wherein R_{10} , R_{11} , R_{12} , R_{13} and R_{14} are each
2 independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl,
3 isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2 .
- 1 78. The compound of claim 59 wherein R_2 is H and R_4 is methyl.
- 1 79. The compound of claim 78 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-CCH$, $-CH=CH-CCH$, or CN.
- 1 80. The compound of claim 50 wherein A is $(C=O)$.
- 1 81. The compound of claim 80 wherein R_4 is methyl.
- 1 82. The compound of claim 81 wherein R_2 is H.
- 1 83. The compound of claim 82 wherein Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl,
2 butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-
3 methoxyphenyl, 2-chlorophenyl, $-C(CH_3)=CH$, 1-(N-pyridyl)ethyl, or 9-fluorenylmethyl.

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84. The compound of claim 83 wherein R₁ is H, Cl, F, dimethylamino, pyrrolidin-1-yl, morpholin-1-yl, 4-methylpiperazin-1-yl, OH or OCH₃; and R₃ is Cl, Br, I, -COOCH₃, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -CCH, -CH=CH-CCH, or CN.

85. A compound of claim 45 selected from the group consisting of:

- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
- 1-[3-Chloro-5-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-dichloro-phenyl)-urea;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(1-phenyl-ethyl)-urea;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-cyano-phenyl)-urea;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-dimethylamino-phenyl)-urea;
- 4-{3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-ureido}-benzoic acid ethyl ester;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-methylsulfanyl-phenyl)-urea;
- 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
- 1-(4-Chloro-phenyl)-3-[3-(4-iodo-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid ethyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-nitro-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 9H-fluoren-9-ylmethyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid allyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid p-tolyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid butyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid benzyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-bromo-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 4-fluoro-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-methoxy-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 2-chloro-phenyl ester;
- [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropenyl ester;

- 29 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid 1-pyridin-1-yl-ethyl
30 ester;
31 [3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-carbamic acid isopropyl ester;
32 5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid
33 methyl ester;
34 1-(4-Fluoro-phenyl)-3-{3-[4-(2-hydroxy-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
35 1-{3-[4-(2-Dimethylamino-ethyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-3-(4-fluoro-
36 phenyl)-urea;
37 1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;
38 1-(4-Chloro-phenyl)-3-[3-(4-ethyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
39 1-(4-Fluoro-phenyl)-3-[3-(2-methyl-4-vinyl-2H-pyrazol-3-yl)-phenyl]-urea;
40 1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-phenyl-2H-pyrazol-3-yl)-phenyl]-urea;
41 1-(4-Chloro-phenyl)-3-{3-[4-(4-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-
42 urea;
43 1-(4-Chloro-phenyl)-3-{3-[4-(3-methoxy-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-
44 urea;
45 1-(4-Chloro-phenyl)-3-{3-[4-(4-fluoro-phenyl)-2-methyl-2H-pyrazol-3-yl]-phenyl}-urea;
46 1-(4-Chloro-phenyl)-3-{3-[2-methyl-4-(4-trifluoromethoxy-phenyl)-2H-pyrazol-3-yl]-
47 phenyl}-urea;
48 1-(4-Chloro-phenyl)-3-[3-(2-methyl-4-thiophen-2-yl-2H-pyrazol-3-yl)-phenyl]-urea;
49 5-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-1-methyl-1H-pyrazole-4-carboxylic acid;
50 1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-
51 urea;
52 1-(3-Chloro-phenyl)-3-[3-(4-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
53 1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-methoxy-phenyl)-urea;
54 1-(4-Chloro-phenyl)-3-[3-(4-ethynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
55 1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-urea;
56 1-[3-(4-But-1-en-3-ynyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-p-tolyl-urea;
57 1-(4-Chloro-phenyl)-3-[3-(4-cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
58 1-[3-(4-Cyano-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;
59 1-[3-(4-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;
60 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-chloro-phenyl)-urea;

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- 61 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-fluoro-
62 benzenesulfonamide;
63 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-bromo-phenyl)-urea;
64 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-isopropyl-phenyl)-urea;
65 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-fluoro-phenyl)-urea;
66 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-methoxy-phenyl)-urea;
67 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(4-cyano-phenyl)-urea;
68 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-4-chloro-
69 benzenesulfonamide;
70 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-fluoro-phenyl]-3-(2,4-dichloro-phenyl)-
71 urea;
72 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-bromo-
73 phenyl)-urea;
74 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-
75 urea;
76 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2,4-dichloro-
77 phenyl)-urea;
78 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-benzamide;
79 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-bromo-
80 phenyl)-urea;
81 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-
82 dimethylamino-phenyl)-urea;
83 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-isopropyl-
84 phenyl)-urea;
85 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-
86 bromo-phenyl)-urea;
87 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-chloro-
88 phenyl)-urea;
89 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-
90 trifluoromethoxy-phenyl)-urea;
91 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-
92 phenyl)-thiourea;

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1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-chloro-phenyl)-urea;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-4-fluorobenzenesulfonamide;

N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-chlorobenzenesulfonamide;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-fluorophenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-chlorophenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2,4-dichlorophenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-dimethylamino-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-methoxy-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(2-phenylcyclopropyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-cyano-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-fluoro-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-isopropyl-phenyl)-urea;

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-phenyl)-urea;

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- 125 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2-
126 phenyl-cyclopropyl)-urea;
- 127 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(2,4-
128 dichloro-phenyl)-urea;
- 129 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-
130 trifluoromethyl-phenyl)-urea;
- 131 1-(3-Amino-4-fluoro-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-
132 yl-phenyl]-urea;
- 133 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-methoxy-
134 phenyl)-urea;
- 135 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-fluoro-3-nitro-
136 phenyl)-urea;
- 137 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-3-(4-cyano-phenyl)-
138 urea;
- 139 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(1-phenyl-ethyl)-
140 urea;
- 141 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(2-phenyl-
142 cyclopropyl)-urea;
- 143 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-chloro-phenyl)-
144 urea;
- 145 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-bromo-
146 phenyl)-urea;
- 147 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-cyano-phenyl)-
148 urea;
- 149 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-dimethylamino-phenyl]-4-fluoro-
150 benzenesulfonamide;
- 151 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-
152 benzenesulfonamide;
- 153 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-morpholin-4-yl-phenyl]-3-(4-methoxy-
154 phenyl)-urea;
- 155 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-(4-methyl-piperazin-1-yl)-phenyl]-3-(4-
156 dimethylamino-phenyl)-urea;

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157 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-isopropyl-
 158 phenyl)-urea;
 159 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-fluoro-phenyl)-urea;
 160 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(3,5-dichloro-phenyl)-
 161 urea;
 162 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-fluoro-phenyl)-urea;
 163 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-4-chloro-
 164 benzenesulfonamide;
 165 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-dimethylamino-
 166 phenyl)-urea;
 167 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-bromo-phenyl)-urea;
 168 N-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-4-chloro-
 169 benzenesulfonamide;
 170 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(3,5-dichloro-phenyl)-
 171 urea;
 172 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-chloro-phenyl)-urea;
 173 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-chloro-phenyl)-urea;
 174 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(2,4-dichloro-phenyl)-
 175 urea;
 176 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-pyrrolidin-1-yl-phenyl]-3-(4-
 177 trifluoromethyl-phenyl)-urea;
 178 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-methoxy-phenyl)-
 179 urea;
 180 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-methoxy-phenyl]-3-(4-methoxy-phenyl)-
 181 urea;
 182 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-5-hydroxy-phenyl]-3-(4-cyano-phenyl)-urea
 183 and
 184 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-phenyl)-thiourea.

1 86. A compound of claim 45 selected from the group consisting of:

- 2 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,4-difluoro-phenyl)-urea;
 3 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
 4 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;

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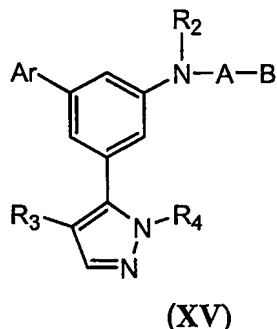
1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-chloro-4-fluoro-phenyl)-urea;
 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-
 phenyl)-urea;
 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-
 phenyl)-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,5-difluoro-phenyl)-urea;
 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3,5-difluoro-phenyl)-urea;
 1-(3-Chloro-4-fluoro-phenyl)-3-[3-(4-chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,4-difluoro-phenyl)-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2,3,4-trifluoro-phenyl)-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-2-trifluoromethyl-
 phenyl)-urea;
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-2-trifluoromethyl-
 phenyl)-urea;
 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-chloro-3-trifluoromethyl-
 phenyl)-urea
 and
 1-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(4-fluoro-3-trifluoromethyl-phenyl)-urea.

87. A compound of claim 45 selected from the group consisting of:

1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(2-chloro-4-trifluoromethyl-
 phenyl)-urea;
 1-(3,4-Bis-trifluoromethyl-phenyl)-3-[3-(4-bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-
 urea;
 3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea;
 1-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-3-(3-fluoro-4-trifluoromethyl-
 phenyl)-urea;
 3-[3-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea;
 3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-chloro-phenyl)-1-methyl-urea
 and
 3-[3-(4-Chloro-2-methyl-2H-pyrazol-3-yl)-phenyl]-1-(4-fluoro-phenyl)-1-methyl-urea.

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1 88. A compound of Formula (XV):



2
3 wherein:

4 i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group
5 consisting of halogen, OR₇, OH, NR₈R₉, carboxy, CN, alkoxycarbonyl, straight chain or
6 branched C₁₋₆ alkyl -C(p)₃, or -O-C(p)₃ where p is halogen;

7 R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or
8 aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four
9 substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃,
10 Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl; or

11 R₈ and R₉ may form part of a 5, 6 or 7 membered cyclic structure which may be
12 either saturated or unsaturated and that may contain up to four heteroatoms selected from
13 O, N or S and said cyclic structure may be optionally substituted by up to four
14 substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe,
15 OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

16 R₇ is H or C₁₋₆ alkyl;

17 R₁₀ is H or C₁₋₆ alkyl;

18 ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

19 iii) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆
20 alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl,
21 straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or
22 heteroaryl groups can be optionally substituted with up to four substituents in any
23 position selected from OH, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is
24 halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be
25 optionally substituted with up to four alkyl substituents in any position;

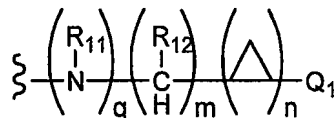
26 iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

27 v) A is C(=O), C(=S) or SO₂;

28 vi) B is L₁ or L₂;

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L₁ is:



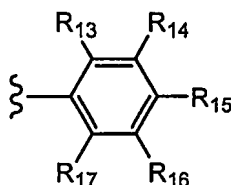
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

Q₁ is:



wherein:

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, halogen, CN, NR₈R₉, COOR₁₀, SR₁₀, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt.

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- 1 89. The compound of claim 88 wherein B is L₁, q is 1, m is 0, and n is 0.
- 1 90. The compound of claim 88 wherein B is L₁, q is 1, m is 1, and n is 0.
- 1 91. The compound of claim 88 wherein B is L₁, q is 1, m is 0, and n is 1.
- 1 92. The compound of claim 88 wherein B is L₁, q is 0, m is 0, and n is 0.
- 1 93. The compound of claim 88 wherein B is L₂.
- 1 94. The compound of claim 89 wherein A is C(=O).
- 1 95. The compound of claim 90 wherein A is C(=O).
- 1 96. The compound of claim 91 wherein A is C(=O).
- 1 97. The compound of claim 92 wherein A is C(=O).
- 1 98. The compound of claim 89 wherein A is C(=S).
- 1 99. The compound of claim 90 wherein A is C(=S).
- 1 100. The compound of claim 91 wherein A is C(=S).
- 1 101. The compound of claim 92 wherein A is C(=S).
- 1 102. The compound of claim 92 wherein A is SO₂.
- 1 103. The compound of claim 88 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.

- 1 104. The compound of claim 88 wherein R_3 is Cl, Br, I, $-\text{COOCH}_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-\text{CCH}$, $-\text{CH}=\text{CH}-\text{CCH}$, or CN.
- 1 105. The compound of claim 94 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.
- 1 106. The compound of claim 94 wherein R_3 is Cl, Br, I, $-\text{COOCH}_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-\text{CCH}$, $-\text{CH}=\text{CH}-\text{CCH}$, or CN.
- 1 107. The compound of claim 95 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.
- 1 108. The compound of claim 95 wherein R_3 is Cl, Br, I, $-\text{COOCH}_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-\text{CCH}$, $-\text{CH}=\text{CH}-\text{CCH}$, or CN.
- 1 109. The compound of claim 96 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl.
- 1 110. The compound of claim 96 wherein R_3 is Cl, Br, I, $-\text{COOCH}_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-\text{CCH}$, $-\text{CH}=\text{CH}-\text{CCH}$, or CN.
- 1 111. The compound of claim 88 wherein R_2 is H and R_4 is methyl.
- 1 112. The compound of claim 103 wherein R_2 is H and R_4 is methyl.
- 1 113. The compound of claim 104 wherein R_2 is H and R_4 is methyl.
- 1 114. The compound of claim 105 wherein R_2 is H and R_4 is methyl.
- 1 115. The compound of claim 106 wherein R_2 is H and R_4 is methyl.
- 1 116. The compound of claim 107 wherein R_2 is H and R_4 is methyl.

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- 1 117. The compound of claim 108 wherein R_2 is H and R_4 is methyl.
- 1 118. The compound of claim 109 wherein R_2 is H and R_4 is methyl.
- 1 119. The compound of claim 110 wherein R_2 is H and R_4 is methyl.
- 1 120. The compound of any of claims 112 through 119 wherein R_{13} , R_{14} , R_{15} , R_{16} and R_{17} are each
2 independently H, F, Cl, Br, CN, dimethylamino, ethoxycarbonyl, methylthio, methyl, ethyl,
3 isopropyl, trifluoromethyl, trifluoromethoxy, methoxy, NH_2 or NO_2 .
- 1 121. The compound of claim 102 wherein R_2 is H and R_4 is methyl.
- 1 122. The compound of claim 121 wherein R_3 is Cl, Br, I, $-COOCH_3$, 2-hydroxyethyl, 2-
2 (dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-methoxyphenyl, 4-fluorophenyl,
3 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, $-CCH$, $-CH=CH-CCH$, or CN.
- 1 123. The compound of claim 93 wherein A is $(C=O)$.
- 1 124. The compound of claim 123 wherein R_4 is methyl.
- 1 125. The compound of claim 124 wherein R_2 is H.
- 1 126. The compound of claim 125 wherein Q_1 is ethyl, 4-nitrophenyl, allyl, 4-methylphenyl, isopropyl,
2 butyl, 2-isopropyl-5-methylcyclohexyl, benzyl, 3-bromophenyl, 4-fluorophenyl, 2-
3 methoxyphenyl, 2-chlorophenyl, $-C(CH_3)=CH$, 1-(N-pyridyl)ethyl, or 9-fluorenylmethyl.
- 1 127. The compound of claim 126 wherein Ar is 4-methoxyphenyl or 4-fluorophenyl; and R_3 is Cl, Br,
2 I, $-COOCH_3$, 2-hydroxyethyl, 2-(dimethylamino)ethyl, vinyl, ethyl, phenyl, 4-methoxyphenyl, 3-
3 methoxyphenyl, 4-fluorophenyl, 4-trifluoromethoxyphenyl, thiophenyl, carboxy, cyclopropyl, -
4 CCH , $-CH=CH-CCH$, or CN.
- 1 128. The compound of claim 88 selected from the group consisting of:

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1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-cyano-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-isopropyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(4-dimethylamino-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-methoxy-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-chloro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-fluoro-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-trifluoromethyl-phenyl)-urea;

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2,4-dichloro-phenyl)-urea;

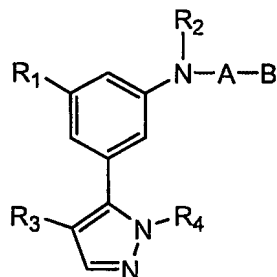
1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-bromo-phenyl)-urea.

1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-methoxy-phenyl)-urea;

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1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-cyano-phenyl)-
 urea;
 1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-isopropyl-
 phenyl)-urea;
 1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(4-dimethylamino-
 phenyl)-urea
 and
 1-[5-(4-Bromo-2-methyl-2H-pyrazol-3-yl)-4'-fluoro-biphenyl-3-yl]-3-(2-phenyl-cyclopropyl)-
 urea.

129. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the
 receptor with a compound of Formula (I):



(I)

wherein:

i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four

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substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl;

R₁₀ is H or C₁₋₆ alkyl;

R₇ is H or C₁₋₆ alkyl;

ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

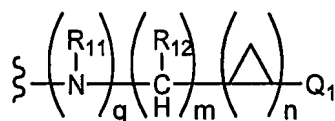
iii) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO₂;

vi) B is L₁ or L₂;

L₁ is:



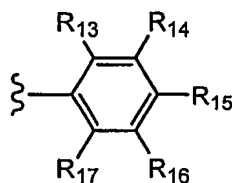
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

Q₁ is:



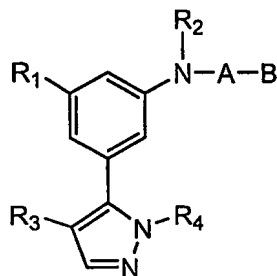
wherein:

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R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, halogen, CN, NR₈R₉, COOR₁₀, SR₁₀, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

130. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the receptor with a compound of Formula (I):



(I)

wherein:

- i) R₁ is H, halogens, NR₅R₆, OH or OR₇, wherein

R₅ and R₆ are independently H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₃R₈, SO₂NR₈R₉, COMe,

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COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl wherein each of the C₃₋₆ cycloalkyl, C₁₋₆ alkyl, or aryl groups may be further optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, CONR₈R₉, NR₈R₉, NHCOCH₃, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, COMe, COEt, CO-lower alkyl, SCF₃, CN, C₂₋₆ alkenyl, H, halogens, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₆ alkyl, and aryl; or

R₅ and R₆ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl;

R₁₀ is H or C₁₋₆ alkyl;

R₇ is H or C₁₋₆ alkyl;

ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

iii) R₃ is halogen, carboxy, CN, alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxy carbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen,

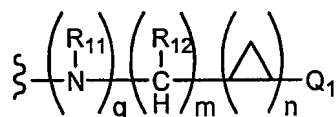
-C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO₂;

vi) B is L₁ or L₂;

L₁ is:



q is 0 or 1;

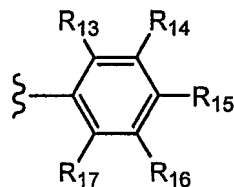
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m is 0 or 1;

n is 0 or 1;

R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

Q₁ is:



wherein:

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, halogen, CN, NR₈R₉, COOR₁₀, SR₁₀, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or

a pharmaceutically acceptable salt; provided that the compound is not any of the following 43 compounds:

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-methoxyphenoxy)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(2-thienyl)carboxamide;

N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)phenyl)amino)carboxamide;

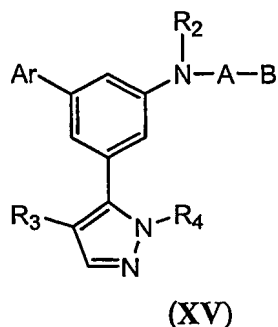
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71 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-trifluoromethoxy)
72 phenyl)methyl)amino)carboxamide;
73 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(1,1-dimethylethoxy)carboxamide;
74 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-trifluoromethoxyphenyl) carboxamide;
75 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)(4-chlorophenyl) carboxamide;
76 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-(trifluoromethoxy) phenyl)acetamide;
77 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-fluorophenyl) acetamide;
78 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(3-methoxyphenyl) acetamide;
79 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-fluorophenyl) acetamide;
80 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(4-nitrophenyl)acetamide;
81 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-2-(2-methoxyphenyl) acetamide;
82 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-methylthiophenyl)amino) carboxamide;
83 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)((4-chlorophenyl)amino) carboxamide;
84 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-fluorophenyl) carboxamide;
85 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-
86 (trifluoromethoxy)phenyl)carboxamide;
87 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-nitrophenyl) carboxamide;
88 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-methoxyphenyl) carboxamide;
89 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-methylphenyl) carboxamide;
90 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(trifluoromethyl)
91 phenyl)carboxamide;
92 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-chlorophenyl) carboxamide;
93 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-chlorophenyl) carboxamide;
94 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-(methylethyl)
95 phenyl)carboxamide;
96 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methoxyphenyl) carboxamide;
97 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3-methylphenyl) carboxamide;
98 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-methyl-N-(4-
99 (trifluoromethoxy)phenyl)-carboxamide;
100 N-(4-(tert-butyl)phenyl)((3-(4-bromo-2-methylpyrazol-3-yl)phenyl) amino)carboxamide;
101 N-(4-(dimethylamino)phenyl)((3-(4-bromo-2-methylpyrazol-3-
102 yl)phenyl)amino)carboxamide;

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103 N-(3,5-dichloro-4-methylphenyl)((3-(4-bromo-2-methylpyrazol-3-
 104 yl)phenyl)amino)carboxamide;
 105 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 106 (trifluoromethylthio)phenyl)carboxamide;
 107 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(cyclohexyl) carboxamide;
 108 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(phenylmethyl) carboxamide;
 109 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-fluorophenyl) carboxamide;
 110 2-(((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-amino)carbonylamino) benzamide;
 111 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-cyanophenyl) carboxamide;
 112 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-cyanophenyl) carboxamide;
 113 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 114 fluorophenylmethyl)carboxamide;
 115 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4-
 116 dimethoxyphenylmethyl)carboxamide;
 117 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(3,4,5-
 118 trimethoxyphenylmethyl)carboxamide;
 119 N-(3-(4-bromo-2-methylpyrazol-3-yl)phenyl)-(((2-methylphenyl)methyl)
 120 amino)carboxamide;
 121 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(4-
 122 methoxyphenylmethyl)carboxamide
 123 and
 124 ((3-(4-bromo-2-methylpyrazol-3-yl)phenyl)amino)-N-(2-(4-
 125 methoxy)phenylethyl)carboxamide.

1 131. A method for modulating the activity of a human 5-HT_{2A} serotonin receptor by contacting the
 2 receptor with a compound of Formula (XV):



3
 4 wherein:

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i) Ar is a phenyl ring optionally substituted with up to five groups selected from the group consisting of halogen, OR₇, OH, NR₈R₉, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl -C(p)₃, or -O-C(p)₃ where p is halogen;

R₈ and R₉ are independently a H, or C₁₋₆ alkyl, or C₂₋₆ alkenyl, or cycloalkyl, or aryl, or CH₂ aryl group and each said group may be optionally substituted by up to four substituents in any position independently selected from halogen, CF₃, OCF₃, OEt, CCl₃, Me, NO₂, OH, OMe, SMe, COMe, CN, COOR₁₀, SO₃R₁₀, COEt, NHCOCH₃, or aryl; or

R₈ and R₉ may form part of a 5, 6 or 7 membered cyclic structure which may be either saturated or unsaturated and that may contain up to four heteroatoms selected from O, N or S and said cyclic structure may be optionally substituted by up to four substituents in any position independently selected from CF₃, CCl₃, Me, NO₂, OH, OMe, OEt, OCF₃, SMe, COOR₁₀, SO₂NR₈R₉, SO₃R₁₀, NHCOCH₃, COEt, COMe, or halogen;

R₇ is H or C₁₋₆ alkyl;

R₁₀ is H or C₁₋₆ alkyl;

ii) R₂ is H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

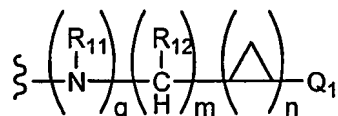
iii) R₃ is halogen, carboxy, CN, alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from OH, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

iv) R₄ is C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

v) A is C(=O), C(=S) or SO₂;

vi) B is L₁ or L₂;

L₁ is:



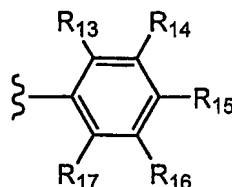
q is 0 or 1;

m is 0 or 1;

n is 0 or 1;

R₁₁ and R₁₂ are each independently H, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, or cycloalkyl;

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Q₁ is:

wherein:

R₁₃, R₁₄, R₁₅, R₁₆ and R₁₇ are each independently H, halogen, CN, NR₈R₉, COOR₁₀, SR₁₀, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl, wherein each of said alkoxycarbonyl, straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₁₀, NR₈R₉, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, and said cycloalkyl, aryl, alkylaryl, arylalkyl or heteroaryl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position;

L₂ is -O-Q₂ wherein Q₂ is straight chain or branched C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, cycloalkyl, aryl, alkylaryl, arylalkyl, wherein each of said cycloalkyl, aryl, alkylaryl, or arylalkyl groups can be optionally substituted with up to four substituents in any position selected from NO₂, OR₇, halogen, -C(p)₃, or -O-C(p)₃ where p is halogen, or an aliphatic or aromatic heterocycle, and said cycloalkyl, aryl, alkylaryl, and arylalkyl groups can alternatively or additionally be optionally substituted with up to four alkyl substituents in any position; or a pharmaceutically acceptable salt.

132. A pharmaceutical composition comprising a compound of any one of the claims 1, 41-45, 88 and 128.

133. A method for the prophylaxis or treatment of reducing platelet aggregation in a patient in need of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.

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- 1 134. A method for the prophylaxis or treatment of any one of the group of indications consisting of
2 coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial
3 fibrillation in a patient in need of said prophylaxis or treatment comprising administering a
4 pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and
5 88 or a pharmaceutical composition according to claim 132.
- 1 135. A method for the prophylaxis or treatment of reducing risk of blood clot formation in an
2 angioplasty or coronary bypass in a surgery patient in need of such prophylaxis or treatment
3 comprising administering a pharmaceutically effective amount of a compound according to any
4 one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claims 132.
- 1 136. A method for the prophylaxis or treatment of reducing risk of blood clot formation in a patient
2 suffering from atrial fibrillation comprising administering to said patient in need thereof a
3 pharmaceutically effective amount of a compound according to any one of claims 1, 41 to 45 and
4 88 or a pharmaceutical composition according to claim 132.
- 1 137. A method for the prophylaxis or treatment of asthma in a patient in need of said prophylaxis or
2 treatment comprising administering a pharmaceutically effective amount of a compound
3 according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to
4 claim 132.
- 1 138. A method for the prophylaxis or treatment of a symptom of asthma in a patient in need of said
2 prophylaxis or treatment comprising administering a pharmaceutically effective amount of a
3 compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition
4 according to claim 132.
- 1 139. A method for the prophylaxis or treatment of agitation or a symptom thereof in a patient in need
2 of said prophylaxis or treatment comprising administering a pharmaceutically effective amount of
3 a compound according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition
4 according to claim 132.
- 1 140. The method of claim 139 wherein said patient is a cognitively intact elderly patient.

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- 1 141. A method for the prophylaxis or treatment of agitation or a symptom thereof in a patient suffering
2 from dementia, comprising administering to said patient in need thereof a pharmaceutically
3 effective amount of a compound according to any one of claims 1, 41 to 45 and 88 or a
4 pharmaceutical composition according to claim 132.
- 1 142. The method of claim 141 wherein said dementia is due to a degenerative disease of the nervous
2 system.
- 1 143. The method of claim 141 wherein said dementia is Alzheimers disease, Lewy Body, Parkinson's
2 disease, or Huntington's disease.
- 1 144. The method of claim 141 wherein said dementia is due to diseases that affect blood vessels.
- 1 145. The method of claim 141 wherein said dementia is due to stroke or multi-infarct dementia.
- 1 146. A method for the prophylaxis or treatment of a behavioral disorder, drug induced psychosis,
2 excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis,
3 psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, or NOS schizophrenia
4 comprising administering to said patient in need thereof a dopamine D2 receptor antagonist and a
5 according to any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to
6 claim 132.
- 1 147. The method of claim 146 wherein said dopamine D2 receptor antagonist is haloperidol.
- 1 148. A method for the prophylaxis or treatment of infantile autism, huntington's chorea, or nausea and
2 vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to said
3 patient in need thereof a dopamine D2 receptor antagonist and a compound according to any one
4 of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.
- 1 149. The method of claim 148 wherein said dopamine D2 receptor antagonist is haloperidol.

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- 1 150. A method for the prophylaxis or treatment of schizophrenia in a patient, comprising administering
2 to said patient in need thereof a dopamine D2 receptor antagonist and a compound according to
3 any one of claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.
- 1 151. The method of claim 150 wherein said dopamine D2 receptor antagonist is haloperidol.
- 1 152. A method for the prophylaxis or treatment of alleviating negative symptoms of schizophrenia
2 induced by the administration of haloperidol to a patient suffering from said schizophrenia,
3 comprising administering to said patient in need thereof a compound according to any one of
4 claims 1, 41 to 45 and 88 or a pharmaceutical composition according to claim 132.
- 1 153. The method of any one of claims 147, 149, 151 and 152 wherein said haloperidol and said
2 compound are administered in separate dosage forms.
- 1 154. The method of any one of claims 147, 149, 151 and 152 wherein said haloperidol and said
2 compound are administered in a single dosage form.
- 1 155. Use of a compound according to any one of claims 1, 41 to 45, 88 and 128 for production of a
2 medicament for use in prophylaxis or treatment of a 5-HT_{2A} related disorder.
- 1 156. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing platelet
2 aggregation in a patient in need of said prophylaxis or treatment.
- 1 157. The use according to claim 155 wherein the 5-HT_{2A} related disorder is any one of the group of
2 indications consisting of coronary artery disease, myocardial infarction, transient ischemic attack,
3 angina, stroke and atrial fibrillation in a patient in need of said prophylaxis or treatment.
- 1 158. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing risk of blood clot
2 formation in an angioplasty or coronary bypass in a surgery patient in need of such prophylaxis or
3 treatment.
- 1 159. The use according to claim 155 wherein the 5-HT_{2A} related disorder is reducing risk of blood clot
2 formation in a patient suffering from atrial fibrillation.

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- 1 160. The use according to claim 155 wherein the 5-HT_{2A} related disorder is asthma.
- 1 161. The use according to claim 155 wherein the 5-HT_{2A} related disorder is agitation.
- 1 162. The use according to claim 155 wherein the 5-HT_{2A} related disorder is dementia.
- 1 163. The use according to claim 155 wherein the 5-HT_{2A} related disorder is Alzheimers disease, Lewy
2 Body, Parkinson's disease, or Huntington's disease.
- 1 164. The use according to claim 155 wherein the 5-HT_{2A} related disorder is a behavioral disorder, drug
2 induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic
3 or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia, or
4 NOS schizophrenia.
- 1 165. The use according to claim 155 wherein the 5-HT_{2A} related disorder is infantile autism,
2 huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies.
- 1 166. The use according to claim 155 wherein the 5-HT_{2A} related disorder is schizophrenia.

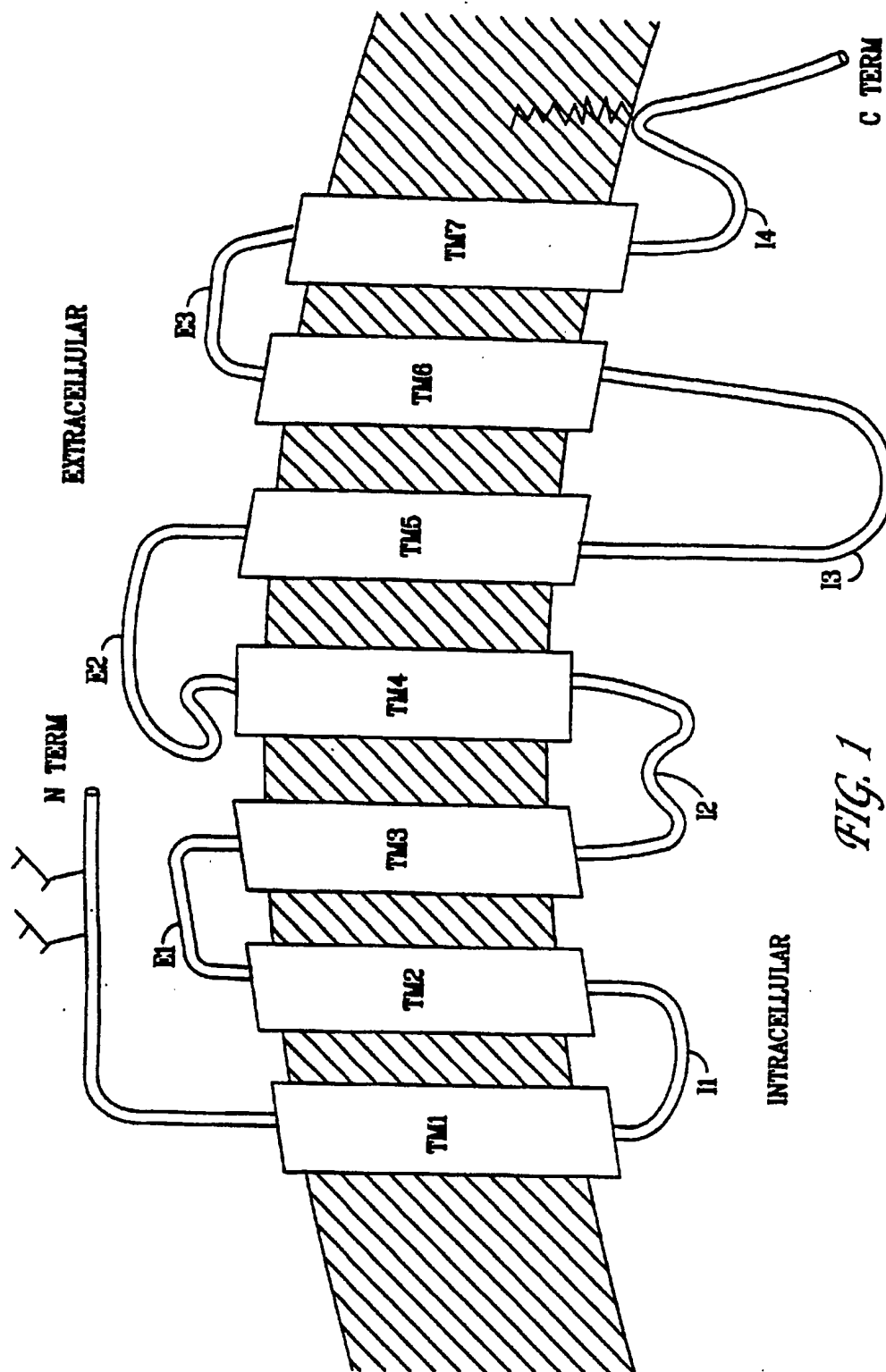


FIG. 1

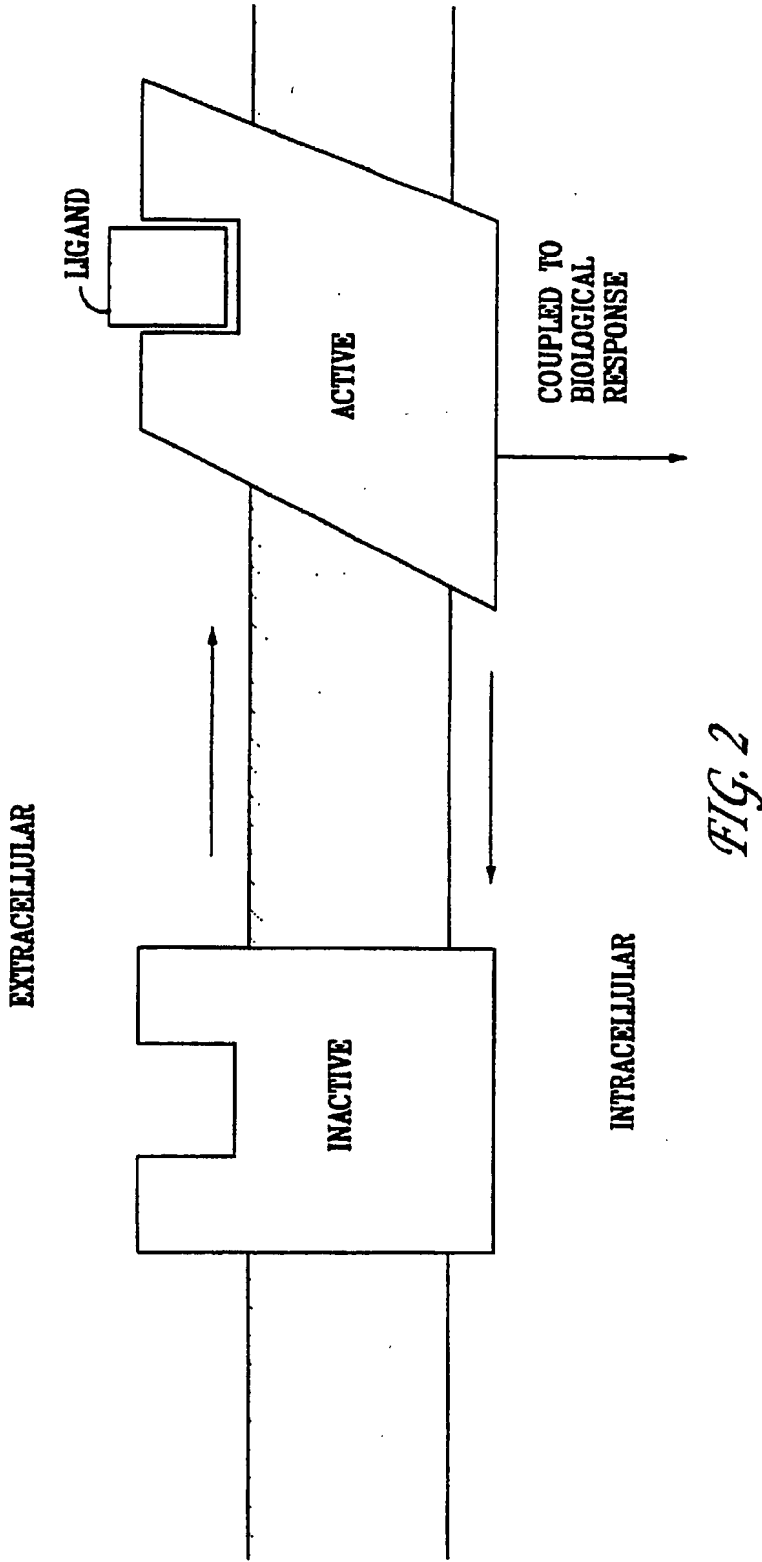


FIG. 3A

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TCGTGTCTCTCCTTACTTCATCTCCAGGAAAAAACTGGTCTGCTTTACTGACAGCCGTAGTGA
TTATTCTAACTATTGCTGGAACATACTCGTCATCATGGCAGTGTCCTAGAGAAAAAGCTGC
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CATGCCCGTGTCCATGTTAACCATCCTGTATGGGTACCGGTGGCCTCTGCCGAGCAAGCTTTGT
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CGCTGGACCGCTACGTGCGCATCCAGAATCCATCCACCACAGCCGCTTCAACTCCAGAACTA
AGGCATTTCTGAAAATCATTGCTGTTTGGACCATATCAGTAGGTATATCCATGCCAATACCAG
TCTTTGGGCTACAGGACGATTGGAAGGTCTTTAAGGAGGGGAGTTGCTTACTCGCCGATGATA
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TTTCTAACTATCAAGTCACTCCAGAAAGAAGCTACTTTGTGTGTAAGTGATCTTGGCACACGG
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GGTCGATCCATAGGGAGCCAGGGTCTACACAGGCAGGAGGACTATGCAGTCCATCAGCAAT
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GCCCTGCTCAATGTGTTTGTGATCGGTTATCTCTCTTCAGCAGTCAACCCACTAGTCTACA
CACTGTTCAACAAGACCTATAGGTCAGCCTTTTCACGGTATATTCAGTGTCAGTACAAGGAAA
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AACTTCAAATGGGACAAAAAAGAATTCAAAGCAAGATGCCAAGACAACAGATAATGACTGC
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GAATGAAAAGGTGAGCTGTGTGTGA

FIG. 3B

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SLHLQEKNSALITAVVILTIAGNILVMAVSLEKKLQATNYFLMSLAIADMLLGFLVMPVSM
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DLGTRAKLASFSFLPQSSLSSEKLFQRSIHREPGSYTGRRTMQSISNEQKACKVLGIVFFLFVVMWC
PFFTINMAVICKESCNEDEVIGALLNVFVWIGYLSSAVNPLVYTLFNKTYRSAFSRYIQCCQYKENKK
PLQLLVNTIPALAYKSSQLQMGQKKNSKQDAKTTDNDCSMVALGKQYSEEASKONSDGVNEKV
SCV

FIG. 4B

MVNLRNAVHSFLVHLIGLLVWQCDSVSPVAAIVTDIFNTSDGGRFKFPDGVQNWPAISIVIIIMTIGGN
ILVIMAVSMEKKLHNATNYFLMSLAIADMLVGLLVMPLSLLAILDYVWPLPRYLCPVWISLDVLFSTASI
MHLCAISLDYVAIRNPIHHSRFNSRTKAIMKIAVWAISIGVSVPIPVIGLRDEEKVFVNNTTCVLNDPN
FVLIGSFVAFFIPLTMVITYCLTIYVLRQALMLLHGHTTEPPGLSLDFLKCCKRNTAEENSANPNQDQ
NARRRKKKERRPRGTMQAINNERKASKVLGIVFFVFLMWCPFFTINILSVLCEKSCNQKIMEKLLNVFVW
IGYVCSGINPLVYTLFNKTYRRAFSNYLCNYKVEKKPPVRQIPRVAATASGRELVNNTYRHTNEPVIEK
ASDNEPGIEMQVENLELPVNPSSVVSERISSV

FIG. 4A

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TACCAGTAAATCCCTCCAGTGTGGTTAGCGAAAGGATTAGCAGTGTGTGA

FIG. 5A

ATGGTGAACCTGAGGAATGCGGTGCATTCATTCCTTGTGCACCTAATTGGCCTATTGGTTTGGCAAT
GTGATATTTCTGTGAGCCCAGTAGCAGCTATAGTAACTGACATTTTCAATACCTCCGATGGTGGACC
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AATAGGTCGCAACATCCTTGTGATCATGGCAGTAAGCATGGAAGAAAGAACTGCACAATGCCACCA
ATTACTTCTTAATGTCCCTAGCCATTGCTGATATGCTAGTGGGACTACTTGTATGCCCTGTCTCTC
CTGGCAATCCTTTATGATTATGTCTGGCCATCAACTAGATATTTGTGCCCGTCTGGATTCTTTAGA
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TCGTGAACAACACGACGTGCGTGCTCAACGACCCAAATTTGCTTCTTATTGGGTCTTCGTAGCTTT
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CCGGTGATCGAGAAAGCCAGTGACAATGAGCCCGGTATAGAGATGCAAGTTGAGAATTTAGAGTT
ACCAGTAAATCCCTCCAGTGTGGTTAGCGAAAGGATTAGCAGTGTGTGA

FIG. 5B

MVNLRNAVHSFLVHLIGLLVWQCDISVSPVAAIVTDIFNTSDGGRFKFPDGVQNWPAISIVIIIMTI
 GGNILVIMAVSMEKKLHNATNYFLMSLAIDMLVGLLVMPLSLLAILDYVWPLPRYLCPVWISL
 DVLFTASIMHLCAISLDRYVAIRNPIEHSRFSRSTKAIMKIAIVWAISIGVSVPIPVIGLRDEEKVFF
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 TAEENSANPNQDQNARRRKKKERRPRGTMQAINNERKAKKVLGIVFFVFLMWCPFFITNLSVL
 CEKSCNQKLMKILLNVFVWIGYVCSGINPLVYTLFNKIYRRAFSNYLRCNYKVEKKPPVRQIPRV
 AATALSGRELNVNIRHTNEPVIEKASDNEPGIEMQVENLELPVNPSSVVSERISSV

FIG. 6B

MDILCEENTSLSTTNSLMQLNDDNRLYSNDFNSGEANTSDAFNWTVDSERNTLSCEGCLSPSCL
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 LTILYGYRWPLPSKLCVWYILDVLFTASIMHLCAISLDRYVAIQNPISHSRFSRSTKAFLKIIAVW
 TISVGISMPFVFGLODDSKVFKEGSCLLADNDFVLIGSFVSFFIPLTMVTYFLTKVLRQALMLL
 HGHTTEPPGLSDFLKCCRN TAEENSANPNQDQNARRRKKKERRPRGTMQAINNERKAS
 KVLGIVFFLFVVMWCPFFITNIMAVICKESCNEVDIGALLNVFVWIGYLSSAVNPLVYTLFNKIYR
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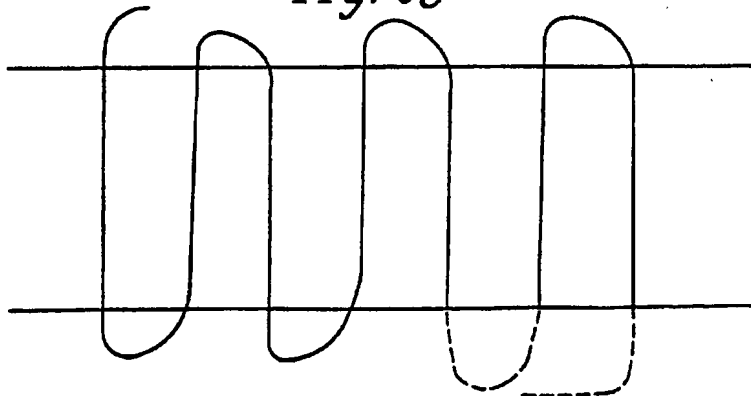
FIG. 6C

FIG. 6A

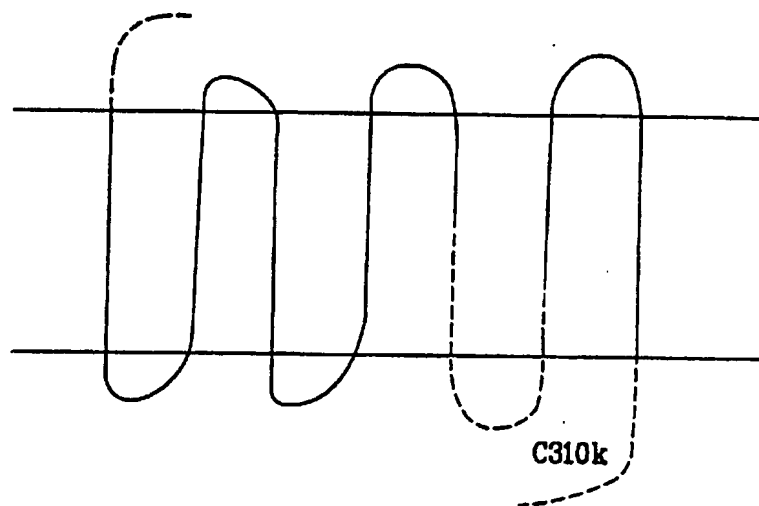
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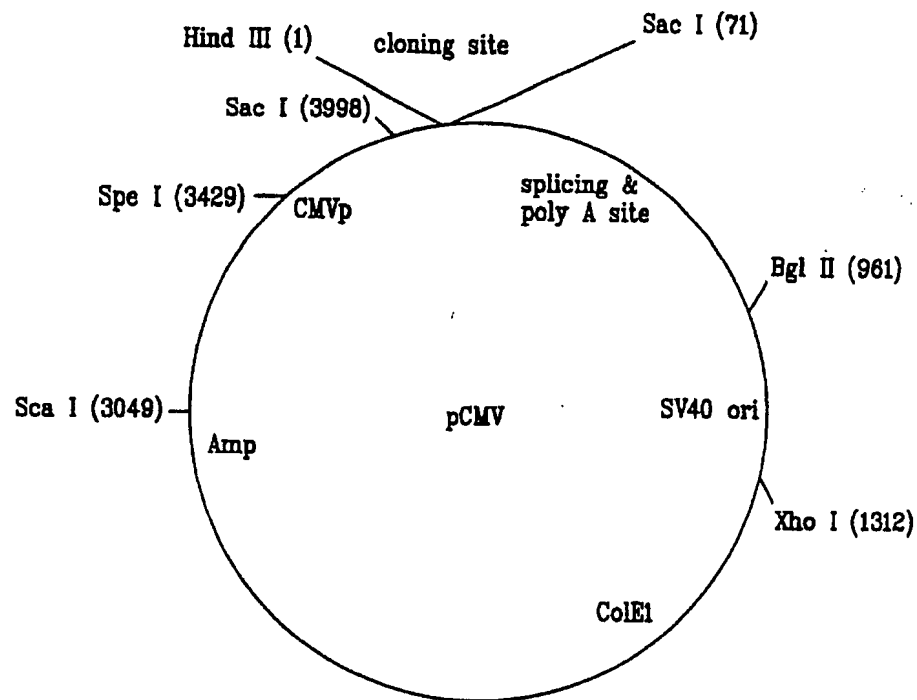
FIG. 7A

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TAGAGATGCAAGTTGAGAATTTAGAGTTACCAGTAAATCCCTCCAGTGTGGTTAGCGAA
AGGATTAGCAGTGTGTGA

FIG. 7B

MDILCEENTSLSSTTNSLMQLNDDNRLYSNDFNSGEANTSDAFNWTVDSENRTNLSCEGCLSPSCL
SLLHLQEKNWSALLTAVVILTIAGNLVIMAVSLEKKLQATNYFLMSLAADMLLGFLVMPVSM
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TISVGISMPIPVGFLQDDSKVFKEGSCILLADDNFVLIGSFVSFFIPLTIMVTITYCLTIYVLRQALML
LHGHTTEPPGLSIDFLKCCKRNTAEENSANPNQDONARRRKKKERRPRGTMQAINNERKA
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RRAFSNYLRCNYKVEKKPPVRQIPRVAATALSGRELVNVIYRHTNEPVIEKASDNEPGIEMQV
ENLELPVNPSWWSERISSV

*FIG. 7C*



- *Xho I (1312) to Sca I (3049) is identical to pRc/RSV Xho I (3045) to 4782.
- *Sca I (3049) to 4070 is identical to pCDM7 Amp Scal (2524) to 3545.
- *multiple cloning site includes Hind III to Sac I of pBluescript II
- *110 to 1312 is identical to pCMD7 Amp 78 to 1278.
- *Sac I and Spe I in MCS are not unique.

FIG. 8

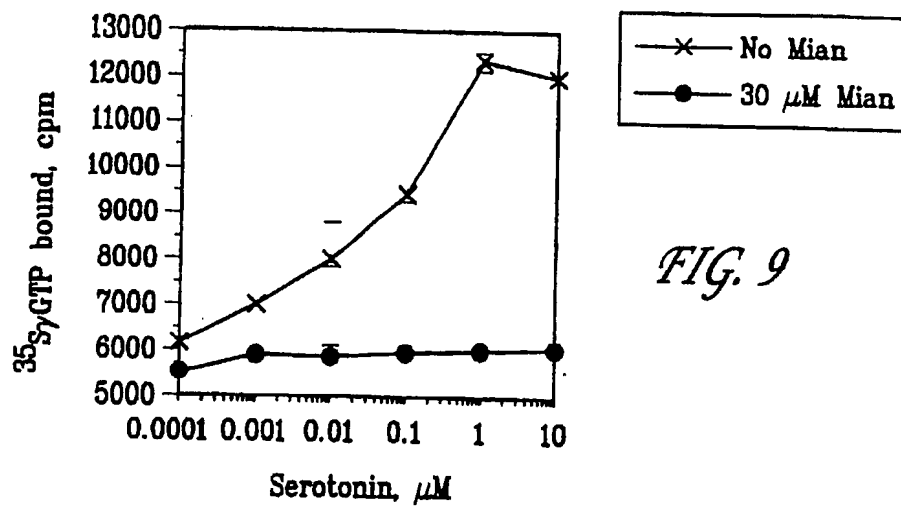


FIG. 9

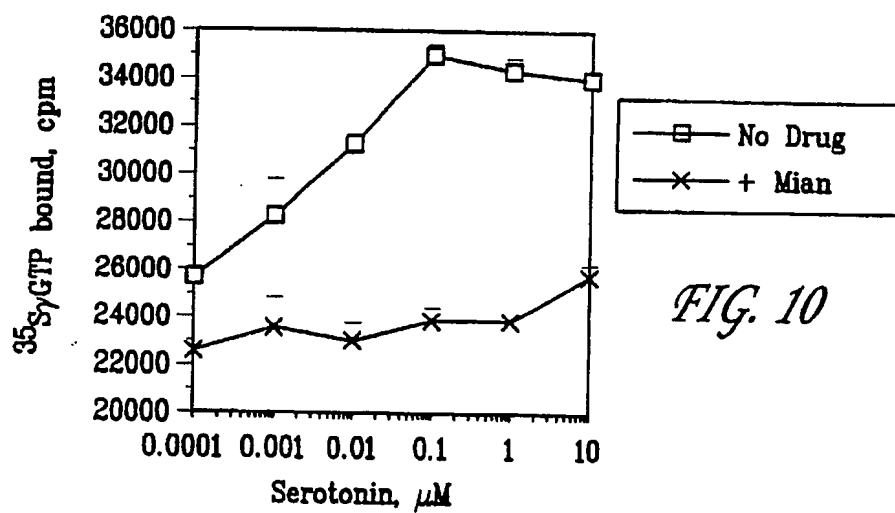


FIG. 10

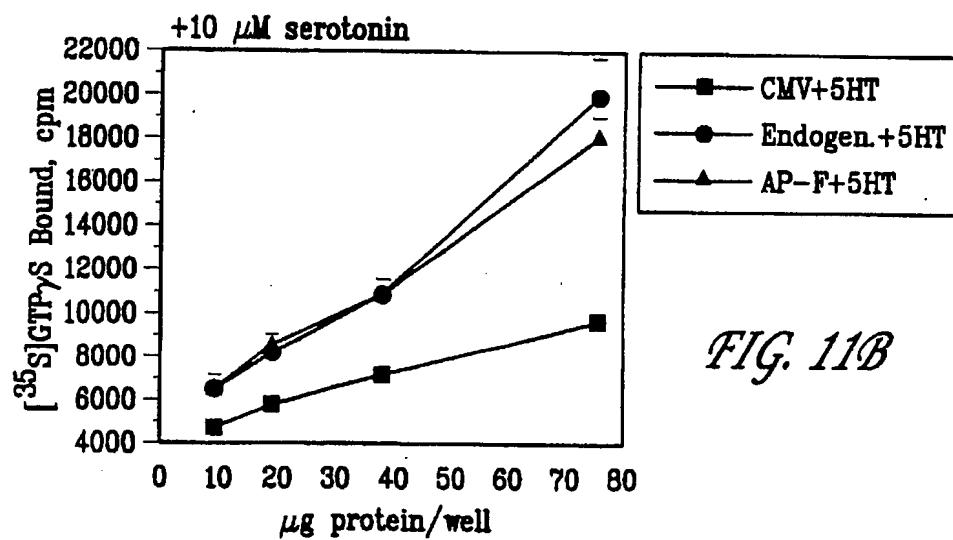
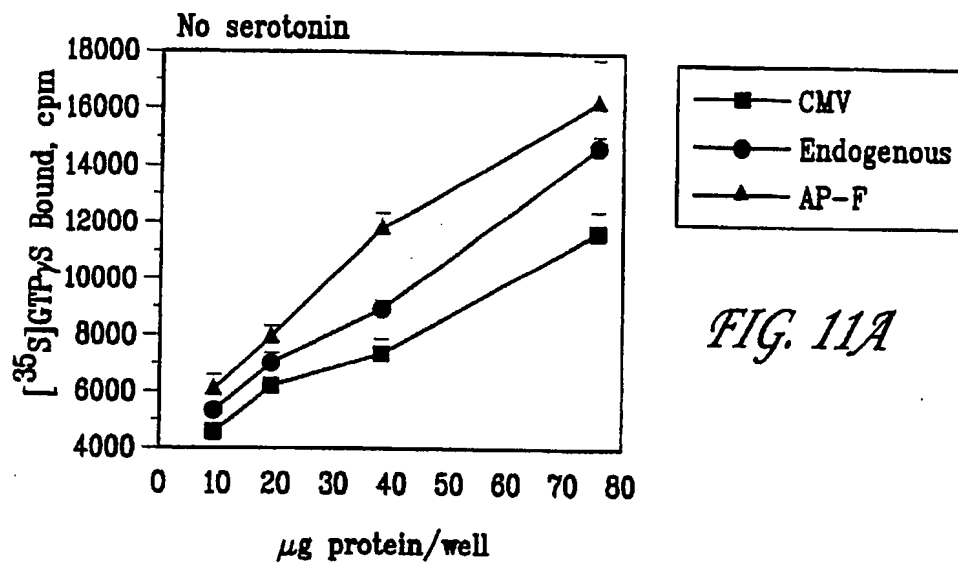
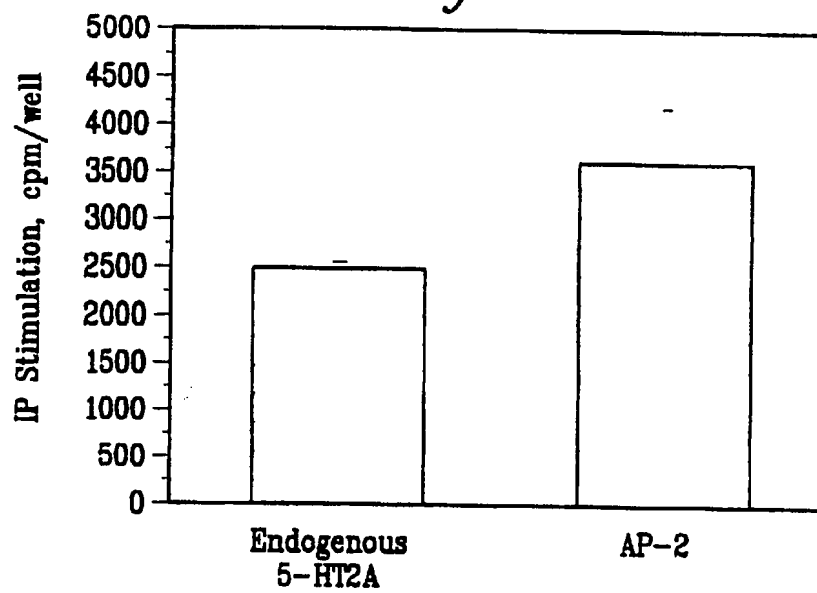
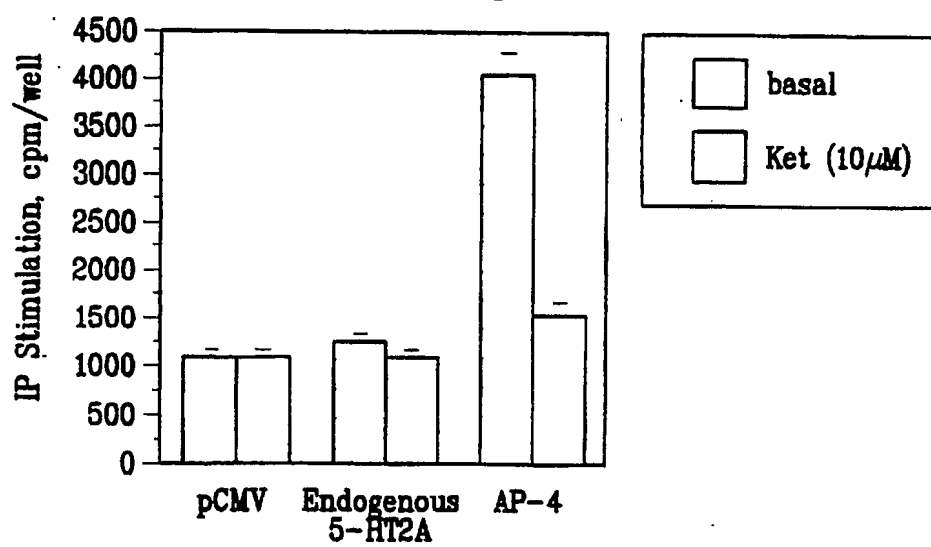
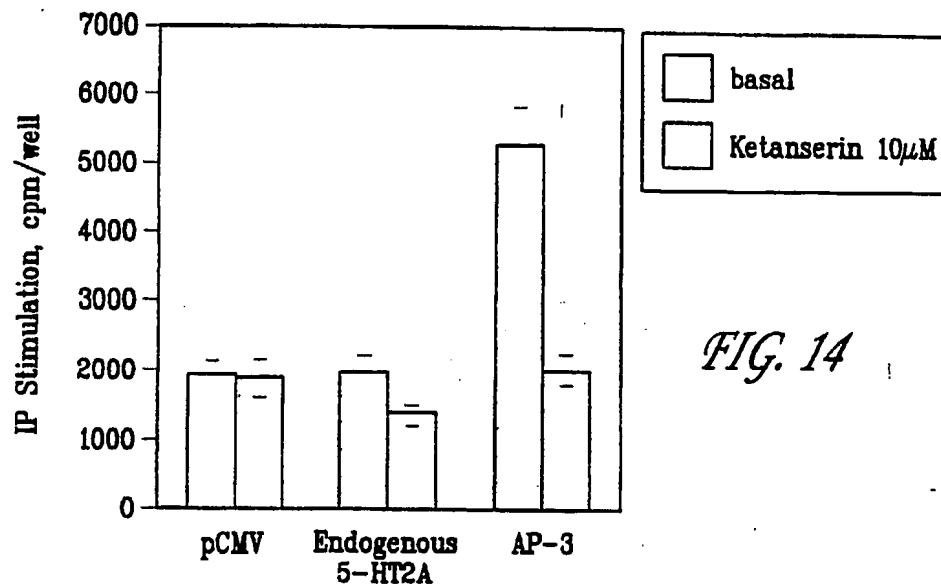
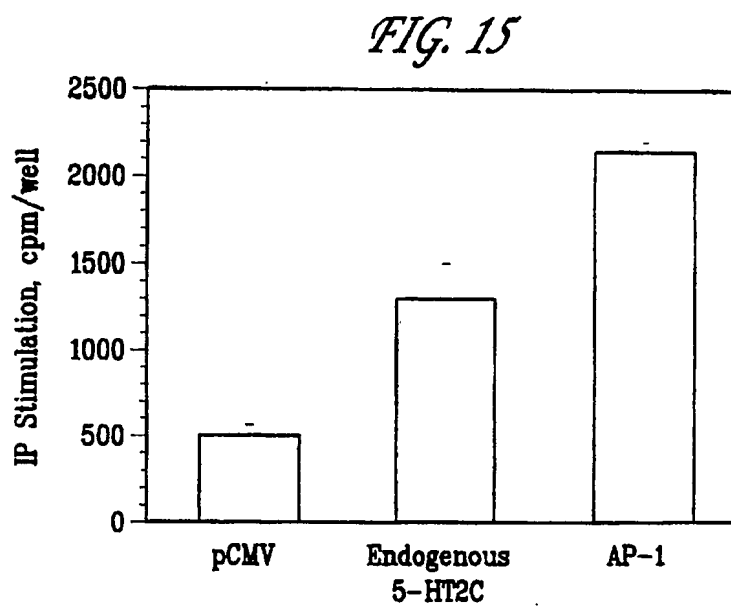


FIG. 12*FIG. 13*

*FIG. 14**FIG. 15*

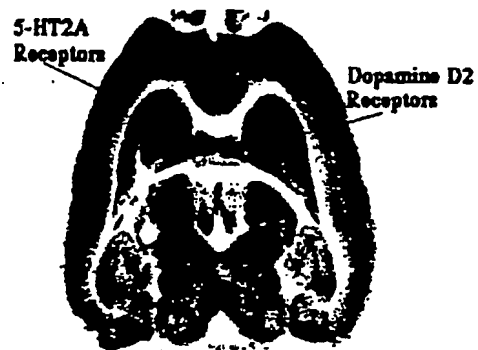
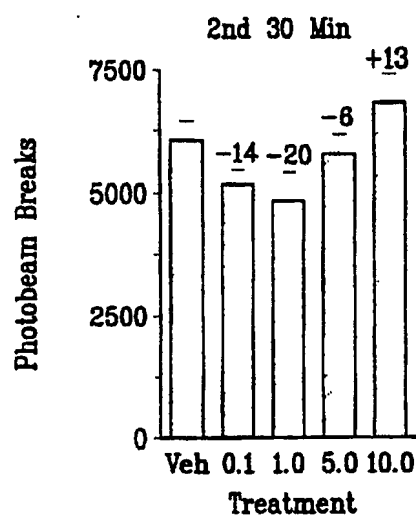
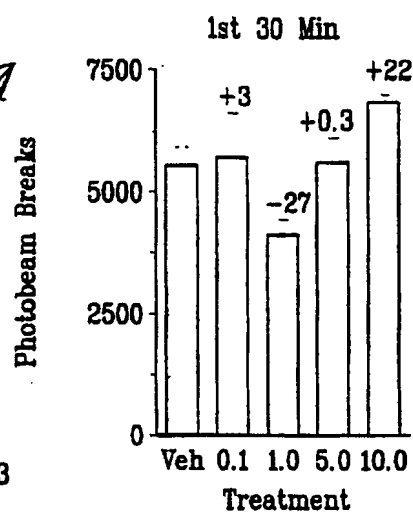
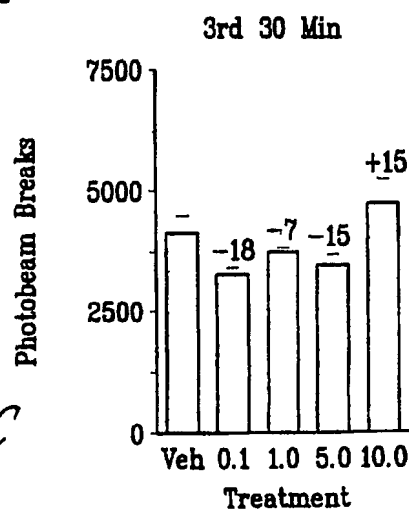
*FIG. 16A**FIG. 16B**FIG. 16C*

FIG. 17A*FIG. 17B**FIG. 17C*

9.WO3
SEQUENCE LISTING

<110> Arena Pharmaceuticals, Inc.
Teegarden, Bradley
Drouet, Keith
Jayakumar, Honnappa
Thomsen, William J.
Maffuid, Paul
Elwell, Katie
Foster, Richard J.
Glen, Robert C.
Lawless, Michael S.
Liu, Qian
Smith, Julian R.
Feichtinger, Konrad

<120> SMALL MOLECULE MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR
USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS
RELATED THERETO

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ttctaactat caaagtactg cgccgacaag ctttgatg 38

<210> 15
<211> 43
<212> DNA
<213> Artificial

<220>
<223> Novel Sequence

9.W03

<400> 15
 ttcagcagtc aaccactag tctatactct gttcaacaaa att 43

<210> 16
 <211> 28
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 16
 atttctagac atatgtagct tgtaccgt 28

<210> 17
 <211> 19
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 17
 atcacctact ttctaacta 19

<210> 18
 <211> 33
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 18
 ccataatcgt caggggaatg aaaaatgaca caa 33

<210> 19
 <211> 33
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 19
 atttttcatt cccctgacga ttatggtgat tac 33

<210> 20
 <211> 33
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 20
 tgatgaagaa agggcaccac atgatcagaa aca 33

<210> 21
 <211> 33
 <212> DNA
 <213> Artificial

9.W03

<220>

<223> Novel Sequence

<400> 21

gatcatgtgg tggcctttct tcatcacaaa cat

33

<210> 22

<211> 1416

<212> DNA

<213> Homo sapien

<400> 22

atggatattc tttgtgaaga aaatacttct ttgagctcaa ctacgaactc cctaattgcaa	60
ttaaattgatg acaacaggct ctacagtaat gactttaact ccggagaagc taacacttct	120
gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaagggtgc	180
ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactgggc tgctttactg	240
acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc	300
ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat	360
atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccatcctgta tgggtaccgg	420
tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg	480
gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc	540
atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg	600
accatatcag taggtatatc catgccaaata ccagtctttg ggctacagga cgattcgaag	660
gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt	720
gtgtcatttt tcattccctt aaccatcatg gtgatcacct actttctaac tatcaagtca	780
ctccagaaag aagctacttt gtgtgtaagt gatcttggca cacggggccaa attagcttct	840
ttcagcttcc tccctcagag ttctttgtct tcagaaaagc tcttcacagc gtcgatccat	900
agggagccag ggtcctacac aggaggagg actatgcagt ccatcagcaa tgagcaaaag	960
gcatgcaagg tgctgggcat cgtcttcttc ctgtttgtgg tgatgtggtg ccctttcttc	1020
atcaciaaaca tcatggccgt catctgcaaa gagtcctgca atgaggatgt cattggggcc	1080
ctgctcaatg tgtttggttg gatcggttat ctctcttcag cagtcaaccc actagtctac	1140
acactgttca acaagacctt taggtcagcc ttttcacggt atattcagtg tcagtacaag	1200
gaaaacaaaa aaccattgca gttaatttta gtgaacacaa taccggcttt ggcctacaag	1260
tctagccaac ttcaaatggg acaaaaaaag aattcaaagc aagatgccaa gacaacagat	1320
aatgactgct caatggttgc tctaggaaag cagtattctg aagaggcttc taaagacaat	1380
agcgacggag tgaatgaaaa ggtgagctgt gtgtga	1416

<210> 23

<211> 471

<212> PRT

<213> Homo sapiens

9.W03

<400> 23

Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
 1 5 10 15
 Ser Leu Met Gln Leu Asn Asp Asp Thr Arg Leu Tyr Ser Asn Asp Phe
 20 25 30
 Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
 35 40 45
 Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
 50 55 60
 Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
 65 70 75 80
 Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
 85 90 95
 Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
 100 105 110
 Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
 115 120 125
 Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
 130 135 140
 Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
 145 150 155 160
 Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
 165 170 175
 Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
 180 185 190
 Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
 195 200 205
 Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
 210 215 220
 Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
 225 230 235 240
 Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Phe Leu
 245 250 255
 Thr Ile Lys Ser Leu Gln Lys Glu Ala Thr Leu Cys Val Ser Asp Leu
 260 265 270

9.W03

Gly Thr Arg Ala Lys Leu Ala Ser Phe Ser Phe Leu Pro Gln Ser Ser
 275 280 285
 Leu Ser Ser Glu Lys Leu Phe Gln Arg Ser Ile His Arg Glu Pro Gly
 290 295 300
 Ser Tyr Thr Gly Arg Arg Thr Met Gln Ser Ile Ser Asn Glu Gln Lys
 305 310 315 320
 Ala Cys Lys Val Leu Gly Ile Val Phe Phe Leu Phe Val Val Met Trp
 325 330 335
 Cys Pro Phe Phe Ile Thr Asn Ile Met Ala Val Ile Cys Lys Glu Ser
 340 345 350
 Cys Asn Glu Asp Val Ile Gly Ala Leu Leu Asn Val Phe Val Trp Ile
 355 360 365
 Gly Tyr Leu Ser Ser Ala Val Asn Pro Leu Val Tyr Thr Leu Phe Asn
 370 375 380
 Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr Ile Gln Cys Gln Tyr Lys
 385 390 395 400
 Glu Asn Lys Lys Pro Leu Gln Leu Ile Leu Val Asn Thr Ile Pro Ala
 405 410 415
 Leu Ala Tyr Lys Ser Ser Gln Leu Gln Met Gly Gln Lys Lys Asn Ser
 420 425 430
 Lys Gln Asp Ala Lys Thr Thr Asp Asn Asp Cys Ser Met Val Ala Leu
 435 440 445
 Gly Lys Gln His Ser Glu Glu Ala Ser Lys Asp Asn Ser Asp Gly Val
 450 455 460
 Asn Glu Lys Val Ser Cys Val
 465 470

<210> 24
 <211> 1377
 <212> DNA
 <213> Homo sapien

<400> 24
 atggtgaacc tgaggaatgc ggtgcattca ttccttgtgc acctaattgg cctattggtt 60
 tggcaatgtg atatttctgt gagcccagta gcagctatag taactgacat tttcaatacc 120
 tccgatggtg gacgcttcaa attcccagac ggggtacaaa actggccagc actttcaatc 180
 gtcatacataa taatcatgac aataggtggc aacatccttg tgatcatggc agtaagcatg 240

9.W03

gaaaagaaac tgcacaatgc caccaattac ttcttaatgt ccctagccat tgctgatatg 300
 ctagtgggac tacttgtcat gccctgtct ctcttgcaa tcctttatga ttatgtctgg 360
 ccactaccta gatatttgtg ccccgctctg atttcttttag atgttttatt ttcaacagcg 420
 tccatcatgc acctctgctg tatatcgctg gatcggatg tagcaatacg taatcctatt 480
 gagcatagcc gtttcaattc gcggactaag gccatcatga agattgctat tgtttgggca 540
 atttctatag gtgtatcagt tcctatccct gtgattggac tgagggacga agaaaagggtg 600
 ttcgtgaaca acacgacgtg cgtgctcaac gacccaaatt tcgttcttat tgggtccttc 660
 gtagctttct tcataccgct gacgattatg gtgattacgt attgcctgac catctacgtt 720
 ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt 780
 ctggatttcc tgaagtgtg caagaggaat acggccgagg aagagaactc tgcaaaccct 840
 aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg 900
 caggctatca acaatgaaag aaaagcttcg aaagtccttg ggattgtttt ctttgtgttt 960
 ctgatcatgt ggtgcccatt ttccattacc aatattctgt ctgttctttg tgagaagtcc 1020
 tgtaaccaa agctcatgga aaagcttctg aatgtgtttg tttggattgg ctatgtttgt 1080
 tcaggaatca atcctctggt gtatctctgt ttcaacaaaa tttaccgaag ggcattctcc 1140
 aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1200
 gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1260
 gaaccggtga tcgagaaagc cagtgacaat gagcccgtga tagagatgca agttgagaat 1320
 ttagagttac cagtaaattc ctccagtgtg gttagcgaag ggattagcag tgtgtga 1377

<210> 25
 <211> 458
 <212> PRT
 <213> Homo sapiens

<400> 25

Met Val Asn Leu Arg Asn Ala Val His Ser Phe Leu Val His Leu Ile
1 5 10 15

Gly Leu Leu Val Trp Gln Cys Asp Ile Ser Val Ser Pro Val Ala Ala
20 25 30

Ile Val Thr Asp Ile Phe Asn Thr Ser Asp Gly Gly Arg Phe Lys Phe
35 40 45

Pro Asp Gly Val Gln Asn Trp Pro Ala Leu Ser Ile Val Ile Ile Ile
50 55 60

Ile Met Thr Ile Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Met
65 70 75 80

Glu Lys Lys Leu His Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala
85 90 95

9.W03

Ile Ala Asp Met Leu Val Gly Leu Leu Val Met Pro Leu Ser Leu Leu
 100 105 110

Ala Ile Leu Tyr Asp Tyr Val Trp Pro Leu Pro Arg Tyr Leu Cys Pro
 115 120 125

Val Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met His
 130 135 140

Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala Ile Arg Asn Pro Ile
 145 150 155 160

Glu His Ser Arg Phe Asn Ser Arg Thr Lys Ala Ile Met Lys Ile Ala
 165 170 175

Ile Val Trp Ala Ile Ser Ile Gly Val Ser Val Pro Ile Pro Val Ile
 180 185 190

Gly Leu Arg Asp Glu Glu Lys Val Phe Val Asn Asn Thr Thr Cys Val
 195 200 205

Leu Asn Asp Pro Asn Phe Val Leu Ile Gly Ser Phe Val Ala Phe Phe
 210 215 220

Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Cys Leu Thr Ile Tyr Val
 225 230 235 240

Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His Thr Glu Glu Pro
 245 250 255

Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys Arg Asn Thr Ala
 260 265 270

Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln Asn Ala Arg Arg
 275 280 285

Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met Gln Ala Ile Asn
 290 295 300

Asn Glu Arg Lys Ala Ser Lys Val Leu Gly Ile Val Phe Phe Val Phe
 305 310 315 320

Leu Ile Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Leu Ser Val Leu
 325 330 335

Cys Glu Lys Ser Cys Asn Gln Lys Leu Met Glu Lys Leu Leu Asn Val
 340 345 350

Phe Val Trp Ile Gly Tyr Val Cys Ser Gly Ile Asn Pro Leu Val Tyr
 355 360 365

9.W03

Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser Asn Tyr Leu Arg
 370 375 380

Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg Gln Ile Pro Arg
 385 390 395 400

Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn Val Asn Ile Tyr
 405 410 415

Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser Asp Asn Glu Pro
 420 425 430

Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro Val Asn Pro Ser
 435 440 445

Ser Val Val Ser Glu Arg Ile Ser Ser Val
 450 455

<210> 26
 <211> 1377
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 26
 atggtgaacc tgaggaatgc ggtgcattca ttccttgtgc acctaattgg cctattgggtt 60
 tggcaatgtg atatttctgt gagcccagta gcagctatag taactgacat tttcaatacc 120
 tccgatggtg gacgcttcaa attcccagac ggggtacaaa actggccagc actttcaatc 180
 gtcatacataa taatcatgac aataggtggc aacatccttg tgatcatggc agtaagcatg 240
 gaaaagaaac tgcacaatgc caccaattac ttcttaatgt ccctagccat tgctgatatg 300
 ctagtgggac tacttgtcat gccctgtct ctcttggaac tcctttatga ttatgtctgg 360
 ccactaccta gatatttgtg ccccgctctg atttcttttag atgttttatt ttcaacagcg 420
 tccatcatgc acctctgcgc tatatcgctg gatcggtatg tagcaatacg taatcctatt 480
 gagcatagcc gtttcaattc gcggactaag gccatcatga agattgctat tgtttgggca 540
 atttctatag gtgtatcagt tcctatccct gtgattggac tgaggggacga agaaaagggtg 600
 ttcgtgaaca acacgacgtg cgtgctcaac gacccaaatt tcgttcttat tgggtccttc 660
 gtagctttct tcataccgct gacgattatg gtgattacgt attgcctgac catctacggt 720
 ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt 780
 ctggatttcc tgaagtgtg caagaggaat acggccgagg aagagaactc tgcaaaccct 840
 aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg 900
 caggctatca acaatgaaag aaaagctaag aaagtccttg ggattgtttt ctttgtgttt 960
 ctgatcatgt ggtgccatt tttcattacc aataattctt ctattctttg tgagaagtcc 1020

9.WO3

tgtaaccaaa agctcatgga aaagcttctg aatgtgtttg tttggattgg ctatgtttgt 1080
 tcaggaatca atcctctggt gtatactctg ttcaacaaaa tttaccgaag ggcattctcc 1140
 aactatattgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1200
 gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1260
 gaaccggtga tcgagaaagc cagtgacaat gagcccgtga tagagatgca agttgagaat 1320
 ttagagttac cagtaaattc ctccagtgtg gtttagcgaag ggattagcag tgtgtga 1377

<210> 27
 <211> 458
 <212> PRT
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 27

Met Val Asn Leu Arg Asn Ala Val His Ser Phe Leu Val His Leu Ile
1 5 10 15

Gly Leu Leu Val Trp Gln Cys Asp Ile Ser Val Ser Pro Val Ala Ala
20 25 30

Ile Val Thr Asp Ile Phe Asn Thr Ser Asp Gly Gly Arg Phe Lys Phe
35 40 45

Pro Asp Gly Val Gln Asn Trp Pro Ala Leu Ser Ile Val Ile Ile Ile
50 55 60

Ile Met Thr Ile Gly Gly Asn Ile Leu Val Ile Met Ala Val Ser Met
65 70 75 80

Glu Lys Lys Leu His Asn Ala Thr Asn Tyr Phe Leu Met Ser Leu Ala
85 90 95

Ile Ala Asp Met Leu Val Gly Leu Leu Val Met Pro Leu Ser Leu Leu
100 105 110

Ala Ile Leu Tyr Asp Tyr Val Trp Pro Leu Pro Arg Tyr Leu Cys Pro
115 120 125

Val Trp Ile Ser Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met His
130 135 140

Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala Ile Arg Asn Pro Ile
145 150 155 160

Glu His Ser Arg Phe Asn Ser Arg Thr Lys Ala Ile Met Lys Ile Ala
165 170 175

Ile Val Trp Ala Ile Ser Ile Gly Val Ser Val Pro Ile Pro Val Ile
 180 185 190

Gly Leu Arg Asp Glu Glu Lys Val Phe Val Asn Asn Thr Thr Cys Val
 195 200 205

Leu Asn Asp Pro Asn Phe Val Leu Ile Gly Ser Phe Val Ala Phe Phe
 210 215 220

Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Cys Leu Thr Ile Tyr Val
 225 230 235 240

Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His Thr Glu Glu Pro
 245 250 255

Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys Arg Asn Thr Ala
 260 265 270

Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln Asn Ala Arg Arg
 275 280 285

Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met Gln Ala Ile Asn
 290 295 300

Asn Glu Arg Lys Ala Lys Lys Val Leu Gly Ile Val Phe Phe Val Phe
 305 310 315 320

Leu Ile Met Trp Cys Pro Phe Phe Ile Thr Asn Ile Leu Ser Val Leu
 325 330 335

Cys Glu Lys Ser Cys Asn Gln Lys Leu Met Glu Lys Leu Leu Asn Val
 340 345 350

Phe Val Trp Ile Gly Tyr Val Cys Ser Gly Ile Asn Pro Leu Val Tyr
 355 360 365

Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser Asn Tyr Leu Arg
 370 375 380

Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg Gln Ile Pro Arg
 385 390 395 400

Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn Val Asn Ile Tyr
 405 410 415

Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser Asp Asn Glu Pro
 420 425 430

Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro Val Asn Pro Ser
 435 440 445

9.W03

Ser Val Val Ser Glu Arg Ile Ser Ser Val
 450 455

<210> 28
 <211> 1437
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 28
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 gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaaggggtgc 180
 ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactgggtc tgctttactg 240
 acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc 300
 ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat 360
 atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccatcctgta tgggtaccgg 420
 tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg 480
 gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc 540
 atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg 600
 accatatcag taggtatata catgccaaata ccagtccttg ggctacagga cgattcgaag 660
 gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt 720
 gtgtcatttt tcattccctt aaccatcatg gtgatcacct actttctaac tatcaagggt 780
 ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt 840
 ctggatttcc tgaagtgtg caagaggaat acggccgagg aagagaactc tgcaaaccct 900
 aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg 960
 caggctatca acaatgaaag aaaagcttcg aaggtagtgg gcatcgtctt cttcctgttt 1020
 gtggtgatgt ggtgcccttt cttcatcaca aacatcatgg ccgtcatctg caaagagtcc 1080
 tgcaatgagg atgtcattgg ggccctgctc aatgtgtttg ttggatcgg ttatctctct 1140
 tcagcagtca acccactagt ctatactctg ttcaacaaaa ttaccgaag ggcattctcc 1200
 aactatttgc gttgcaatta taaggtagag aaaaagcctc ctgtcaggca gattccaaga 1260
 gttgccgcca ctgctttgtc tgggagggag cttaatgtta acatttatcg gcataccaat 1320
 gaaccggtga tcgagaaagc cagtgacaat gagcccgtga tagagatgca agttgagaat 1380
 ttagagttac cagtaaattc ctccagtgtg gttagcgaaa ggattagcag tgtgtga 1437

<210> 29
 <211> 478
 <212> PRT
 <213> Artificial

<220>

9.W03

<223> Novel Sequence

<400> 29

Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn
 1 5 10 15

Ser Leu Met Gln Leu Asn Asp Asp Asn Arg Leu Tyr Ser Asn Asp Phe
 20 25 30

Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
 35 40 45

Ser Glu Asn Arg Thr Asn Leu Ser Cys Glu Gly Cys Leu Ser Pro Ser
 50 55 60

Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
 65 70 75 80

Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
 85 90 95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
 100 105 110

Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
 115 120 125

Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
 130 135 140

Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
 145 150 155 160

Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
 165 170 175

Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
 180 185 190

Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
 195 200 205

Pro Ile Pro Val Phe Gly Leu Gln Asp Asp Ser Lys Val Phe Lys Glu
 210 215 220

Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
 225 230 235 240

Val Ser Phe Phe Ile Pro Leu Thr Ile Met Val Ile Thr Tyr Phe Leu
 245 250 255

9.W03

Thr Ile Lys Val Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His
 260 265 270

Thr Glu Glu Pro Pro Gly Leu Ser Leu Asp Phe Leu Lys Cys Cys Lys
 275 280 285

Arg Asn Thr Ala Glu Glu Glu Asn Ser Ala Asn Pro Asn Gln Asp Gln
 290 295 300

Asn Ala Arg Arg Arg Lys Lys Lys Glu Arg Arg Pro Arg Gly Thr Met
 305 310 315 320

Gln Ala Ile Asn Asn Glu Arg Lys Ala Ser Lys Val Leu Gly Ile Val
 325 330 335

Phe Phe Leu Phe Val Val Met Trp Cys Pro Phe Phe Ile Thr Asn Ile
 340 345 350

Met Ala Val Ile Cys Lys Glu Ser Cys Asn Glu Asp Val Ile Gly Ala
 355 360 365

Leu Leu Asn Val Phe Val Trp Ile Gly Tyr Leu Ser Ser Ala Val Asn
 370 375 380

Pro Leu Val Tyr Thr Leu Phe Asn Lys Ile Tyr Arg Arg Ala Phe Ser
 385 390 395 400

Asn Tyr Leu Arg Cys Asn Tyr Lys Val Glu Lys Lys Pro Pro Val Arg
 405 410 415

Gln Ile Pro Arg Val Ala Ala Thr Ala Leu Ser Gly Arg Glu Leu Asn
 420 425 430

Val Asn Ile Tyr Arg His Thr Asn Glu Pro Val Ile Glu Lys Ala Ser
 435 440 445

Asp Asn Glu Pro Gly Ile Glu Met Gln Val Glu Asn Leu Glu Leu Pro
 450 455 460

Val Asn Pro Ser Ser Val Val Ser Glu Arg Ile Ser Ser Val
 465 470 475

<210> 30
 <211> 1437
 <212> DNA
 <213> Artificial

<220>
 <223> Novel Sequence

<400> 30
 atggatattc ttgtgaaga aaatacttct ttgagctcaa ctacgaactc cctaatagcaa 60
 ttaaatagatg acaacaggct ctacagtaat gactttaact ccaagaagc taacacttct 120

9.W03

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gatgcattta actggacagt cgactctgaa aatcgaacca acctttcctg tgaaggggtgc 180
ctctcaccgt cgtgtctctc cttacttcat ctccaggaaa aaaactgggtc tgctttactg 240
acagccgtag tgattattct aactattgct ggaaacatac tcgtcatcat ggcagtgtcc 300
ctagagaaaa agctgcagaa tgccaccaac tatttcctga tgtcacttgc catagctgat 360
atgctgctgg gtttccttgt catgcccgtg tccatgttaa ccacccctgta tgggtaccgg 420
tggcctctgc cgagcaagct ttgtgcagtc tggatttacc tggacgtgct cttctccacg 480
gcctccatca tgcacctctg cgccatctcg ctggaccgct acgtcgccat ccagaatccc 540
atccaccaca gccgcttcaa ctccagaact aaggcatttc tgaaaatcat tgctgtttgg 600
accatatcag taggtatatc catgccaata ccagtctttg ggctacagga cgattcgaag 660
gtctttaagg aggggagttg cttactcgcc gatgataact ttgtcctgat cggctctttt 720
gtgtcatttt tcattcccct gacgattatg gtgattacgt attgcctgac catctacgtt 780
ctgcgccgac aagctttgat gttactgcac ggccacaccg aggaaccgcc tggactaagt 840
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aaccaagacc agaacgcacg ccgaagaaag aagaaggaga gacgtcctag gggcaccatg 960
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Asn Ser Gly Glu Ala Asn Thr Ser Asp Ala Phe Asn Trp Thr Val Asp
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Cys Leu Ser Leu Leu His Leu Gln Glu Lys Asn Trp Ser Ala Leu Leu
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Thr Ala Val Val Ile Ile Leu Thr Ile Ala Gly Asn Ile Leu Val Ile
 85 90 95

Met Ala Val Ser Leu Glu Lys Lys Leu Gln Asn Ala Thr Asn Tyr Phe
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Leu Met Ser Leu Ala Ile Ala Asp Met Leu Leu Gly Phe Leu Val Met
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Pro Val Ser Met Leu Thr Ile Leu Tyr Gly Tyr Arg Trp Pro Leu Pro
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Ser Lys Leu Cys Ala Val Trp Ile Tyr Leu Asp Val Leu Phe Ser Thr
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Ala Ser Ile Met His Leu Cys Ala Ile Ser Leu Asp Arg Tyr Val Ala
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Ile Gln Asn Pro Ile His His Ser Arg Phe Asn Ser Arg Thr Lys Ala
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Phe Leu Lys Ile Ile Ala Val Trp Thr Ile Ser Val Gly Ile Ser Met
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Gly Ser Cys Leu Leu Ala Asp Asp Asn Phe Val Leu Ile Gly Ser Phe
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Thr Ile Tyr Val Leu Arg Arg Gln Ala Leu Met Leu Leu His Gly His
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Val Asn Pro Ser Ser Val Val Ser Glu Arg Ile Ser Ser Val
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Organization
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Published:

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(88) Date of publication of the international search report:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SMALL MOLECULE MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE PROPHYLAXIS AND TREATMENT OF DISORDERS RELATED THERETO

(57) Abstract: The present invention relates to certain pyrazole derivatives of Formula (I) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Formula (I): Compounds and pharmaceutical compositions thereof are directed to methods useful in the prophylaxis or treatment of reducing platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or a symptom, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorder, psychosis, acute schizophrenia, chronic schizophrenia and NOS schizophrenia and related disorders. The present invention also relates to the method of prophylaxis or treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with a dopamine D₂ receptor antagonist such as haloperidol, administered separately or together.



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/02059

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/16 C07D231/14 C07D231/12 C07D401/12 C07D409/04
A61K31/415 A61K31/4155 A61P7/02 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 52927 A (SMITH JULIAN R; FOSTER RICHARD J (GB); ARENA PHARMACEUTICALS INC) 21 October 1999 (1999-10-21) page 31, line 8 -page 37, line 9 page 39 -page 45 page 47 -page 49, line 4 page 51 -page 54 claims 14-20	1-166
A	WO 98 24785 A (KATO MASAYUKI; NODA YUKA (JP); SPEARS GLEN W (JP); HARADA KEIKO (J) 11 June 1998 (1998-06-11) claims 1,2,5-8; examples	1,45,88, 129-166
A	US 5 281 571 A (MISCHKE DEBORAH A ET AL) 25 January 1994 (1994-01-25) claims 1-3	1,45,88
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

B document member of the same patent family

Date of the actual completion of the international search

2 October 2003

Date of mailing of the international search report

10/10/2003

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Hass, C

INTERNATIONAL SEARCH REPORT

I tional Application No

PCT/US 03/02059

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 02 076464 A (ARENA PHARMACEUTICALS INC; MENZAGHI FREDERIQUE (US); BEHAN DOMINIC) 3 October 2002 (2002-10-03)</p> <p>claims</p>	<p>1-3, 7, 8, 16-21, 24-30, 33, 45-47, 51, 52, 60-65, 68-74, 77, 129, 130, 132-166</p>

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US 03/02059

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 129-131, 133-154 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/02059

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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Information on patent family members

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	21/64		B 2 G 0 4 5
			F 2 G 0 5 4
	21/78	21/78	C
	33/483	33/483	C
審査請求 有 請求項の数 6 O L (全 6 頁) 最終頁に続く			

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(71) 出願人 396020800

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最終頁に続く

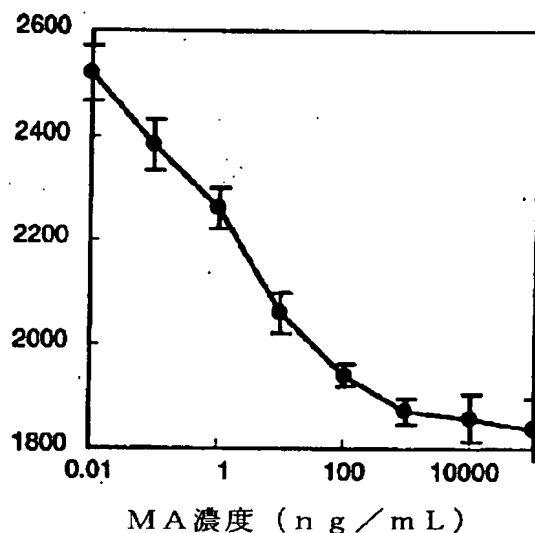
(54) 【発明の名称】 新規な蛍光プローブ類、これらを組み合わせたメタンフェタミンの測定キットおよびメタンフェ

(57) 【要約】 タミンの簡易測定法

【課題】 高感度で、簡易なメタンフェタミンの測定手段の提供

【解決手段】 蛍光共鳴エネルギー移動を利用した競合ホモジニアス時間分解蛍光イムノアッセイ方法によるメタンフェタミンの測定方法およびCy 5またはCy 3にメタンフェタミン抗体を共有結合した蛍光プローブと、BPTAまたはBHHCT-RM³⁺錯体、ここでRMはEu、Sm、Tbなどの希土類金属にメタンフェタミン-プロテイン結合体を共有結合した構造を含む蛍光プローブとの組み合わせからなる前記メタンフェタミンの測定方法に用いるキット。

蛍光 (Cy5)



【特許請求の範囲】

【請求項1】 蛍光共鳴エネルギー移動を利用した競合ホモジニアス時間分解蛍光イムノアッセイ方法によるメタンフェタミンの測定方法。

【請求項2】 Cy5またはCy3にメタンフェタミン抗体を共有結合した蛍光プローブと、BHHCTまたはBPTA- RM^{3+} 錯体（ここでRMは希土類金属）にメタンフェタミン-プロテイン結合体を共有結合した蛍光プローブとの組み合わせからなる請求項1に記載のメタンフェタミンの測定方法に用いるキット。

【請求項3】 Cy5またはCy3にメタンフェタミン抗体を共有結合した蛍光プローブ、ビオチン化メタンフェタミン、およびストレプトアビジン-BHHCTまたはBPTA- RM^{3+} 錯体（ここでRMは希土類金属）との組み合わせからなる請求項1に記載のメタンフェタミンの測定方法に用いるキット。

【請求項4】 Cy5またはCy3とメタンフェタミン抗体とが共有結合した請求項1に記載のメタンフェタミンの測定方法に用いる蛍光プローブ。

【請求項5】 BHHCTまたはBPTA- RM^{3+} 錯体（ここでRMは希土類金属）にメタンフェタミン-プロテイン結合体を共有結合した構造を含む請求項1に記載のメタンフェタミンの測定方法に用いる蛍光プローブ。

【請求項6】 プロテインがウシ血清アルブミン、キーホールリンペットヘモシアニン（KLH）、サイログロブリン、または合成ポリアミン類であることを特徴とする請求項4に記載の蛍光プローブ。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】 本発明は、時間分解蛍光イムノアッセイ方法により高感度でメタンフェタミン（以下、MAと表現する場合もある。）を検出する方法、特に、新規な蛍光共鳴エネルギー移動（Fluorescence Resonance Energy Transfer、FRET）現象を示す蛍光プローブの組み合わせ、具体的には、

1、メタンフェタミンをプロテイン（例えばBSA）-BHHCTまたはBPTA- RM^{3+} 錯体（ここで、RMは希土類金属）で標識した蛍光プローブとCy5またはCy3にメタンフェタミン抗体を共有結合した蛍光プローブまたは

2、ストレプトアビジン-BHHCTまたはBPTA- RM^{3+} 錯体（ここで、RMは希土類金属）と組み合わせたビオチン化メタンフェタミンと、更にCy5またはCy3にメタンフェタミン抗体を共有結合した蛍光プローブとを組み合わせ用いた、競合ホモジニアス時間分解蛍光イムノアッセイ方法による簡易で高感度のメタンフェタミンの測定方法、ならびに該測定方法に用いる新規なキットおよび蛍光プローブ類に関する。

【0002】

【従来の技術】 ある希土類錯体は強い蛍光を発するこ

と、これらの希土類錯体は通常の有機蛍光色素とは異なり、紫外光で（ $\sim 330\text{nm}$ ）で励起され、希土類の持つ特異な発光現象により蛍光を発生するため、蛍光寿命が数百マイクロ秒から2ミリ秒と極めて長いという特徴を持つことが良く知られている。特に希土類として Eu^{3+} 、 Tb^{3+} を用い、これに適当な配位子を用いて錯体化した蛍光材料は、蛍光特性を持つ測定材料として、また適当なプロテインと化学結合、例えば共有結合させて抗体としての機能を用いた蛍光プローブとして利用されてきている。

【0003】 このような蛍光を利用した測定技術の発展の中で、本発明者らも優れた発光特性を示す希土類錯体、具体的には配位子として4座配位 β -ジケトン型配位子BHHCT〔4, 4'-ビス（1'', 1'', 1'', 2'', 2'', 2''-ヘプタフロロ-4'', 6''-ヘキサベンジオン-6''-イル）クロロスルフォ- α -テトラフェニル〕またはBPTA〔N, N, N', N''-（2, 6-ビス（3'-アミノメチル-1'-ピラゾリル）-4-フェニルピリジン）テトラキス（アセティックアシッド）〕を用いた Eu^{3+} 錯体を見出している。そして、該錯体をメタンフェタミンの時間分解蛍光イムノアッセイのラベリング剤として利用することを発表している（Kimura, H., Yuan, J., Wang, G., Matsumoto, K. and Mukaida, M. J Anal Toxicol, 23, 11-16, 1999,）。更に前記ラベリング剤を適当なプロテイン、例えばBSA（ウシ血清アルブミン）に結合させて蛍光プローブを作成し、該蛍光プローブを時間分解蛍光イムノアッセイの蛍光試薬とすることについても既に提案している（Yuan, J., Matsumoto, K. and Kimura, H., Anal Chem, 70, 596-601, 1998,）。

【0004】 時間分解蛍光イムノアッセイは、パルス励起光照射後、一定の時間をおいて非特異的な蛍光バックグラウンドが減衰した後、ラベル剤に由来する特定波長の長寿命蛍光のみを測定する方法であり、高感度分析が可能になることが知られている。しかしながら、現在用いられている Eu 錯体のラベル剤は蛍光強度が十分でないという欠点があった。前記本発明者らの新しいラベル剤は比較のおだやかな条件でプロテインを直接標識でき、強い蛍光と安定性をもつのが特徴である。また、2000年10月5、6日コクヨホールにおいて開催された「単一分子・原子レベルの反応制御」第4回シンポジウムの講演要旨集（前記開催日に頒布）第35頁～36頁において、BPTA- Tb^{3+} 錯体をドナーとしてCy3をアクセプターとする共鳴エネルギー移動を利用する均一溶液でのDNAハイブリダイゼーションアッセイについてはすでに報告されていることを述べている。しかしながら、BSA-BHHCT- Eu^{3+} 錯体とCy5とを組み合わせで蛍光共鳴エネルギー移動を利用してメタンフェタミンを時間分解蛍光イムノアッセイによる定量分析することについては全く報告されていない。ただ、

BPTA-Tb³⁺とCy 3をそれぞれドナーおよびアクセプターの組合せとして用いて分析を行ったことを、前記予稿集において報告している。因みに、蛍光共鳴エネルギー移動 (Fluorescence Resonance Energy Transfer, FRET) とは、ある2つの蛍光化合物が距離的に近い位置 (およそ100 Å以内) に存在するとき、その2つの蛍光物質のうちの片方 (ドナーと呼ばれる) の発光スペクトルと他方 (アクセプターと呼ばれる) の励起スペクトルが重なりを持つ場合、ドナー励起波長の光を当てると、本来観察されるはずのドナーの蛍光が減衰し、代わりにアクセプターの蛍光が強化 (エネルギーの移動により) されて観察される現象であることが知られており、蛍光を用いた分析法において、ドナー側の蛍光が小さくなり、アクセプターの蛍光が増幅されるので、蛍光増幅分析法に利用されている。

【0005】

【発明が解決しようとする課題】本発明は、メタンフェタミンをより高感度で、容易に測定する方法を提供することである。本発明者らは前記のように種々の蛍光プローブの組み合わせを用いて、被測定物を高感度で測定できる方法を開発してきた。その中で、メタンフェタミンを測定 (定性的および定量的) できる蛍光プローブの組み合わせ、特に被測定物であるメタンフェタミンと競合し、蛍光共鳴エネルギー移動による蛍光増幅特性を持ち、かつ、感度が1 ng/mLでホモジニアス (均一溶液系) イムノアッセイが可能な時間分解蛍光プローブの組み合わせを見出すことができ、前記課題を解決することができた。

【0006】

【課題を解決するための手段】本発明の第1は、蛍光共鳴エネルギー移動を利用した競合ホモジニアス時間分解蛍光イムノアッセイ方法によるメタンフェタミンの測定方法である。本発明の第2は、Cy 5またはCy 3にメタンフェタミン抗体を共有結合した蛍光プローブと、BHHCTまたはBPTA-RM³⁺錯体 (ここでRMは希土類金属) にメタンフェタミン-プロテイン結合体を共有結合した蛍光プローブとの組み合わせからなる請求項1に記載のメタンフェタミンの測定方法に用いるキットである。本発明の第3は、Cy 5またはCy 3にメタンフェタミン抗体を共有結合した蛍光プローブ、ビオチン化メタンフェタミン、およびストレプトアビジン-BHHCTまたはBPTA-RM³⁺錯体 (ここでRMは希土類金属) との組み合わせからなる請求項1に記載のメタンフェタミンの測定方法に用いるキットである。第4の発明は、Cy 5またはCy 3とメタンフェタミン抗体とが共有結合しなる請求項1に記載のメタンフェタミンの測定方法に用いる蛍光プローブである。または第5の発明は、BHHCTまたはBPTA-RM³⁺錯体 (ここでRMは希土類金属) にメタンフェタミン-プロテイン結合体を共有結合した構造を含む前記メタンフェタミンの

測定方法に用いる蛍光プローブであり、好ましくは、プロテインがウシ血清アルブミン、キーホールリンペットヘモシアニン (KLH)、サイログロブリン、または合成ポリアミン類であることを特徴とする前記メタンフェタミンの測定方法に用いる蛍光プローブである。

【0007】

【本発明の実施の態様】本発明をより詳細に説明する。

A. Cy 5またはCy 3 (Amersham Life Science社の登録商標) にメタンフェタミン (MA) 抗体を共有結合したメタンフェタミンの測定方法に用いる蛍光プローブについて。該プローブは、ウサギなどに免疫して作製した抗体、例えば、抗MA抗体であるウサギ免疫グロブリン (IgG) に有機色素である蛍光シアニン (fluorescing cyanine、Cy 5またはCy 3、Amersham Life Science社から市販されている。) を標識することにより得られる。Cy 5の吸収極大波長は643 nmであり、Cy 3の吸収極大波長は550 nmである。

【0008】B. BPTAまたはBHHCT-RM³⁺錯体 (ここでRMは希土類金属) とメタンフェタミン-プロテイン結合体とを共有結合した構造を含むメタンフェタミンの測定方法に用いる蛍光プローブは、例えば、N-アミノブチルMAと適当なプロテイン、例えばウシ血清アルブミンとの結合体 (MA-BSA) に前記公知のBPTAまたはBHHCT-RM³⁺錯体でラベリングすることによって得られる。BPTA-Tb³⁺錯体の蛍光極大波長は543 nmであるが、Cy 3の吸収波長域と530 nm~560 nmの領域で重なる。また、BHHCT-Eu³⁺錯体の蛍光極大波長は615 nmであるが、該蛍光波長域はCy 5の吸収波長域と605 nm~625 nmの領域で重なる。

【0009】C. 蛍光共鳴エネルギー移動については、前記したとおりである。ドナー蛍光体の発光領域とアクセプター蛍光体の吸収領域 (励起波長域) が充分な重なりがあり、かつ前記発光部位-吸収部位とが充分に蛍光共鳴エネルギー移動が可能にドナー-アクセプターの結合構造 (前記エネルギー移動が可能な近接領域にあるような) が設計されていることが、競合ホモジニアス系での分析を可能にする条件である。したがって、抗MA抗体としては、ウサギIgG、ヤギIgG、マウスIgGなどを好ましいものとして挙げるができる。また、MAに結合する前記プロテインとしては、BSA、キーホールリンペットヘモシアニン (KLH)、サイログロブリン、ストレプトアビジン、合成ポリアミン類などを好ましいものとして挙げるができる。

【0010】D. また、測定法としては、蛍光測定用マイクロタイタープレートに標識抗原、例えば、MA-BSA-BHHCT-Eu³⁺を配置し、MA (被検出物) 標準液 (検量線作成) または検体液または希釈液、さらにCy 5標識抗体溶液を同時に加えて混合し、適当な温度、例えば37℃で、適当な時間、例えば30分反応さ

せる。ドナー蛍光プローブの励起波長、例えば、MA-BSA-BHHCT-Eu³⁺の場合340nmでEu³⁺を励起し、アクセプターの発光、例えば抗MA抗体-Cy5の場合、680nmの蛍光強度を時間分解蛍光測定(遅延時間;50マイクロ秒、遅延時間後測定時間(window time);400マイクロ秒)で測定される。

【0011】

【実施例】使用機器;時間分解蛍光測定器としてはARVO SX (ワラックベルトールジャパン社製)を用いた。

【0012】実施例1

N-アミノブチルMAとBSAの結合体(MA-BSA)にEu³⁺蛍光ラベル剤(BHHCT-Eu³⁺)を標識し抗原を、抗MA抗体に対してMAを競合させて反応させる。前記抗MA抗体は、ウサギに免疫して作製した抗体(抗MAウサギIgG)に蛍光有機色素であるCy5(図5)(Amersham Life Scienceの商品名)を標識することにより作成した。エネルギードナーである前記BHHCT-Eu³⁺の蛍光ピーク波長615nmは、エネルギーアクセプターであるCy5の吸収ピーク波長の643nmに近く、前記蛍光波長領域と吸収波長領域に十分な重なりがあり、前記ドナーの励起光である紫外光で励起されることにより、BHHCT-Eu³⁺錯体からのエネルギー移動が起こり、アクセプターであるCy5は増感発光した。

【0013】蛍光測定用マイクロタイタープレートに標識抗原であるMA-BSA-BHHCT-Eu³⁺を25μL配置し、被検体であるMAの標準液または検体希釈液50μL、さらにCy5標識抗体溶液25μLを同時に加えて混合し、37℃で30分反応させた。前記標識抗原のBHHCT-Eu³⁺錯体の励起波長340nmでBHHCT-Eu³⁺を励起し、MA-Cy5の蛍光極大値680nmにおけるCy5の蛍光強度を時間分解蛍光測定で求めた。

【0014】緩衝液(0.05Mトリスヒドロキシメチルアミノメタン-HCl緩衝液、pH7.4)中の標準MAの最小検出濃度は、第1図のCy5の発光とMA濃度との相関を示す検量線から約0.1ng/mLの感度で測定可能であった。また、濃度範囲1ng/mL~1μg/mLの濃度範囲で測定可能であった。測定誤差は8濃度の平均CV(coefficient of variation、再現性を示す。)が1.98%であった。

【0015】実施例2

次に検体である尿や血清が測定に及ぼす影響を調べるために、覚せい剤を含まないことが明らかなヒトの尿および血清を100倍(■)、20倍(▲)、10倍(×)、5倍(*)希釈および未希釈(●)したものに、MAを10⁻²~10⁻²ng/mLの濃度になるように加えた。これらの尿および血清について前記Cy5およびEu³⁺のそれぞれの蛍光強度を測定し、緩衝液で希

釈したMA溶液の測定値との比較を行った(図2a、2b)。Cy5の蛍光強度で表したMAの標準曲線は図2に示すように尿や血清の濃度が高くなる(希釈率が下がる)ほどCy5の蛍光強度が下がり、また、検量線の傾きも小さくなった。この原因のひとつは図3a、bに示すようにエネルギードナーであるEu³⁺の蛍光強度が尿や血清の濃度に依存して下がっていることによる。

【0016】MAの競合剤であるMA-BSA-BHHCT-Eu³⁺は一定の濃度で加えているので、Eu³⁺の蛍光強度は理論的に一定であるはずであるが、被検物のバッファーによる希釈度により異なることが前記測定により理解される。しかし図3a、bからも明らかなように、被検体(被測定成分)であるフリーMAの濃度には依存しない、換言すればMAの測定に影響しないことを示す。また、図2および3から、Eu³⁺の蛍光強度は尿や血清を100倍に希釈した時はほとんど影響を受けないが、未希釈検体の場合は緩衝液の時の約85~50%程度にまで減少することが分かった。

【0017】これに対し、次にEu³⁺の発光による励起エネルギーを受け取るアクセプターのCy5の蛍光の受ける影響を調べた。図4a、4b[バッファー(□)、MAが、0.01ng/mL(◇)、0.1(○)、1(△)、10(■)、100(◆)]にはCy5/Eu³⁺の蛍光強度比が尿や血清の濃度によってどのような変化を示すかを表している。尿や血清を含まない緩衝液でのCy5/Eu³⁺の値を100%とすると、未希釈の尿や血清では約90%に下がっている。また、血清に血球を加えて溶血させ、溶血血清がどのような影響を与えるかについても検討した。溶血血清は溶血を含まない血清に較べると明らかにEu³⁺の消光を強くしたが、Cy5/Eu³⁺の割合は溶血していない血清と変わらなかった。これらの結果から、検体条件によるCy5の消光、あるいはエネルギー遷移の効率がほとんど影響を受けていないことが理解できる。ホモジニアスアッセイでは検体のもつ様々な夾雑物が影響することが予測されたが、同率希釈のMAを含まない尿や血清で検量線をひけば種々の検体条件においても、メタフェタミンを測定できることが理解された。

【0018】実施例3

前記知見に基づいて、覚せい剤使用者の尿検体20について蛍光共鳴エネルギー移動を利用した競合ホモジニアス時間分解蛍光イムノアッセイ方法によるメタフェタミンを測定し、その測定結果とガスクロマトグラフィーの測定値と比較したところ、相関係数r=0.94と高い相関が得られた。本発明の方法は全く洗浄操作を必要とせず、30分で測定結果が得られるので、簡便迅速なMA測定方法として有効であることが分かった。他の薬剤のスクリーニング手段としても本手法が適用できることが予測できる。

【0019】

【発明の効果】以上述べたように、本発明により、メタンフェタミンの簡単で、高感度の測定が可能になった、という優れた効果がもたらされる。更に、他の薬剤のスクリーニング手段としても十分に本手法が適用できることが予測できることから、今後の高感度で、簡易な種々の薬剤の測定手段の確立に貢献すること大である。

【図面の簡単な説明】

【図1】 Cy 5の発光とMA濃度との相関を示す検量線

【図2】 検体である尿(a)や血清(b)のCy 5の蛍光によるMAの測定におよぼす影響〔100倍

(■)、20倍(▲)、10倍(×)、5倍(*)希釈および未希釈(●)〕

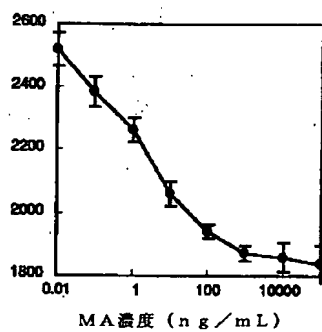
【図3】 検体である尿(a)や血清(b)のEu³⁺の蛍光強度におよぼす影響〔100倍(■)、20倍(▲)、10倍(×)、5倍(*)希釈および未希釈(●)〕

【図4】 Cy 5/Euの蛍光強度比と尿や血清の濃度の相関〔バッファー(□)、MAが、0.01 ng/mL(◇)、0.1(○)、1(△)、10(■)、100(◆)〕

【図5】 Cy 5の化学構造

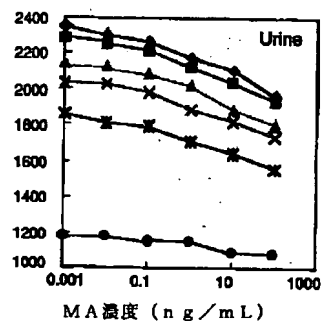
【図1】

蛍光 (Cy5)

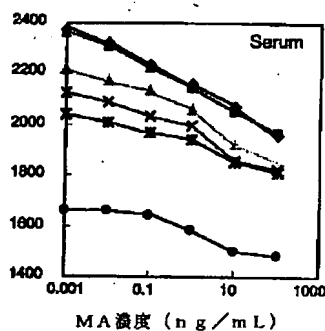


【図2】

a 蛍光 (Cy5)

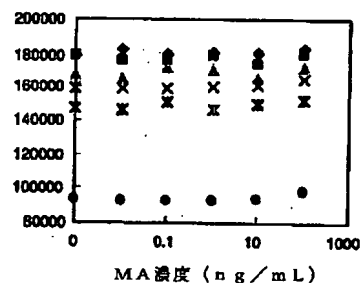


b 蛍光 (Cy5)

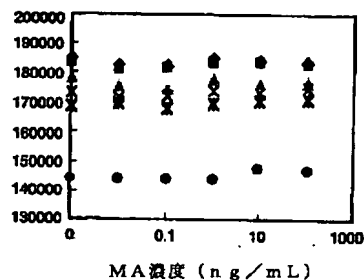


【図3】

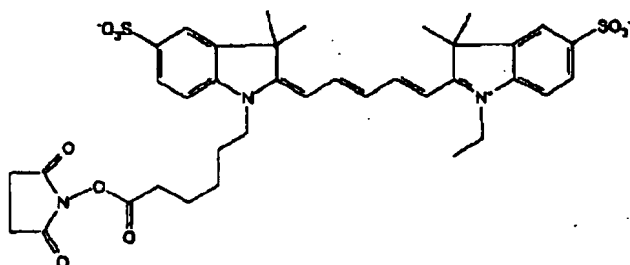
a 蛍光 (Eu)



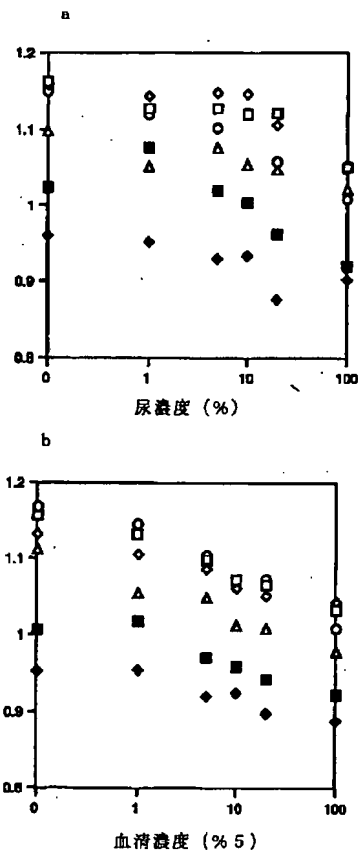
b 蛍光 (Eu)



【図5】



【図4】



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